Archives of Neurology and Psychiatry

VOLUME 27 MAY, 1932 NUMBER 5

LISSAUER'S DEMENTIA PARALYTICA

A CLINICAL AND PATHOLOGIC STUDY

H. HOUSTON MERRITT, M.D.
Fellow of the National Research Council
BOSTON
AND
M. SPRINGLOVA, M.D.
Assistant in the Czechoslovakian Psychiatric Clinic, Prague
PRAGUE, CZECHOSLOVAKIA

The usual case of dementia paralytica shows at autopsy diffuse atrophy of the cerebral cortex, which is most intense in the frontal lobes and progressively decreases in intensity toward the posterior poles of the hemispheres. Such a distribution of the atrophy is expected from the character of the clinical course, which offers no symptoms or signs of a focal nature. In contrast to these usual cases are the cases which during life show focal signs and at autopsy striking atrophy of certain convolutions. It is the purpose of this study to review the reports of such cases found in the literature and to report the clinical and pathologic observations in eight cases from the Deutsche Forschungsanstalt in Munich, in an effort to determine in what manner they differ from the usual cases of dementia paralytica. We wish also to report several observations that are characteristic of these cases and have not formerly been reported or well studied. The most important of these is the loss of myelin in the white matter. Heretofore, dementia paralytica has been considered only a disease of the cortex, and all lesions found in the white matter have usually been thought to be secondary. It is our purpose to show that lesions which are independent of the cortical changes occur in the white matter in cases of dementia paralytica.

REVIEW OF CASES PREVIOUSLY PUBLISHED

The first thorough studies of atypical cases of dementia paralytica were made by Lissauer and Storch [1] and by Alzheimer,[2] who suggested

Submitted for publication, Oct. 5, 1931.

From the Deutsche Forschungsanstalt für Psychiatrie (Kaiser Wilhelm Institute), Munich.

1. Lissauer, H., and Storch, E.: Ueber einige Fälle atypischer progressiver Paralyse, Monatschr. f. Psychiat. u. Neurol. **9**:401, 1901.

2. Alzheimer, A.: Histologische Studien zur Differentialdiagnose der progressiven Paralyse, in Nissl: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1904, vol. 1.

that these cases be called Lissauer's dementia paralytica. Table 1 shows a summary of the clinical and pathologic observations in the thirty-five [3] cases that we have found recorded in the literature.[4] With the exception of the cases of Lissauer and Storch,[1] those reported before the appearance of Alzheimer's [2] famous study of dementia paralytica are of somewhat doubtful value. Clinically, their cases were characterized by the following facts: The ages of the patients varied between 59 and 30 years, with an average of 40 years, and the proportion of males to females was about 5:1. These figures agree with those for the usual cases of dementia paralytica. The duration of the disease in these cases was four years, which is somewhat longer than for the usual cases. The most constant clinical characteristics were the occurrence of apoplectiform or epileptiform attacks and the presence of neurologic signs of a localizing nature. All the cases except one showed attacks of an apolectiform or epileptiform nature, and in twenty-two of the thirty cases of patients who were subject to epileptiform attacks, the attacks were at times unilateral. In all of the cases except one signs indicative of localized lesions, such as hemiplegia, aphasia, apraxia, hemianopia, etc., were present.

Pathologically, the cases were characterized by macroscopically apparent atrophy of certain convolutions, which in all of the cases, with the exception of those of Buder [4] and Bielschowsky,[4] were in the so-called posterior portion of the hemisphere. The atrophic process involved both hemispheres in only three cases. The phrase "posterior

3. Seven additional cases were reported by Starlinger (footnote 4, last reference), but as the pathologic reports of these cases were confined to studies of the pyramidal tract, they were not suitable for this study.

4. Ascher, B.: Ueber Aphasie bei allgemeiner Paralyse, Allg. Ztschr. f. Psychiat. **49**:256, 1893. Ballet, G., cited by Alzheimer (footnote 2). Bielschowsky, M.: Ueber Markfleckenbildung und spongiösen Schichtenschwund in der Hirnrinde der Paralytiker, J. f. Psychol. u. Neurol. **25**:72, 1920. Boedeker and Juliusburger: Anatomische Befunde bei Dementia paralytica, Neurol. Centralbl. **16**:774, 1897. Brie: Ueber Herdsymptome bei progressiver Paralyse, Allg. Ztschr. f. Psychiat. **48**:682, 1892. Buder, T.: Einseitige Grosshirnatrophie mit gekreuzter Kleinhirnatrophie bei einem Fall von progressiver Paralyse mit Herderscheinungen, Allg. Ztschr. f. Psychiat. **60**:534, 1903. Fischer, O.: Der spongiöse Rindenschwund, ein besonderer Destruktionprozess der Hirnrinde, Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:1, 1911. Heilbronner: Rindenbefunde bei progressiver Paralyse, Allg. Ztschr. f. Psychiat. **53**:172, 1897. Köppen, M.: Beiträge zum Studium der Hirnrindenerkrankungen, Arch. f. Psychiat. **28**:931, 1896. Mönkemöller: Zur Lehre von den Herdsymptomen bei Dementia paralytica, Allg. Ztschr. f. Psychiat. **57**:814, 1900. Muratow, W.: Ueber die protrahierten corticalen Krämpfe bei der allgemeinen Paralyse der Irren, Neurol. Centralbl. **16**:194, 1897. Selvili, P. D.: Zur pathologischen Anatomie der Dementia paralytica, Zurich, 1876. Starlinger, J.: Beitrag zur pathologischen Anatomie der progressiven Paralyse, Monatschr. f. Psychiat. u. Neurol. **7**:1, 1900.

TABLE 1.—*Summary of the Clinical Observations and Location of the Atrophy in Thirty-Five Cases of Lissauer's*

TABLE 1.—*Summary of the Clinical Observations and Location of the Atrophy in Thirty-Five Cases of Lissauer's Dementia Paralytica Reported in the Literature*

Author	Age	Sex	Duration of Case, Years	Clinical Data: Attacks: Apoplectiform	Clinical Data: Attacks: Epileptiform	Clinical Data: Localizing Symptoms: Hemiplegia	Clinical Data: Localizing Symptoms: Aphasia	Clinical Data: Localizing Symptoms: Other	Localization of Atrophy†
Selvili	..	..	..	..	+	Right	..	.....	Left Ca.
Brie	..	..	..	..	+*	.....	..	.....	Left Cp.
Ascher	45	M	2	..	?	.....	+	.....	Left T.
Heilbronner									
Case 1	..	..	..	..	+*	Left	..	.....	Right Ca., Cp.
Case 2	..	..	..	..	+*	Left	..	.....	Right Ca., Cp.
Köppen									
Case 1	43	F	..	..	+*	.....	+	.....	Left Cp., T., P.
Case 2	41	M	2	+	+*	Left	+	.....	Left and right O., T.
Muratow									
Case 1	45	M	..	0	+*	Right	+	.....	Left Ca., Cp.
Case 2	55	M	1	+	+*	Left	0	Left hemianesthesia	Right Ca., Cp.
Boedecker and Juliusburger									
Case 1	45	M	2½	..	+*	Left	..	Left hemianesthesia	Right Ca., Cp.
Case 2	38	M	..	..	+*	Left	..	Left hemianesthesia	Right Ca., Cp.
Case 3	54	M	..	..	+*	Left	..	Left hemianesthesia	Right Ca., Cp.
Ballet	..	..	..	..	..	.....	+	.....	Left Broca
Mönkemöller	39	F	1½	+	+*	Left	..	Left hemianesthesia	Left Ca., Cp., P.
Starlinger	41	M	2	..	+*	Right	..	.....	Left Ca., Cp., T1.
Lissauer									
Case 1	49	M	8	..	+*	Right	+	Deafness	T., I.
Case 2	46	M	3½	+	0	Right	0	Right astereognosis	Left Cp., P.
Case 3	47	M	2	+	+*	Left and right	0	Left hemianesthesia	Left F., right T., O.
Case 4	40	M	..	+	+	Left	0	Left hemianopia; deafness	Right T., P., O.
Buder	53	M	2	+	+*	Right	+	.....	Left F., Ca., Cp.
Alzheimer									
Case 1	41	M	3	+	+*	Left	0	0	Right Ca., Cp., P.
Case 2	37	M	2	+	+*	Right	0	Hemianesthesia	Left F., T., Ca., Cp., P.
Case 3	43	M	3½	+	+*	Left	+	.....	Right F., Ca., Cp., P.
Case 4	46	M	..	0	0	0	+	.....	Right I., T., P.
Case 5	39	M	3	+	+*	Right	+	.....	Left Cp., T., I., P.
Case 6	43	M	2	+	+*	Right	+	Cortical deafness	Left Ca., Cp., T1., I., P.
Case 7	41	M	14	0	+	Right	0	.....	Left Ca., Cp., T1., P.
Case 8	59	M	7	+	0	Right	+	Right hemianopia	Left T., P., O.
Fischer									
Case 1	30	M	4	0	+*	.....	+	Apraxia	Left T1.
Case 2	38	F	..	0	+	.....	+	.....	Left T.
Case 3	43	M	2	0	+	Right	+	.....	Left Ca., Cp., T., P.
Case 4	40	M	5	+	0	Right	+	.....	Left Ca., Cp., T., P.
Case 5	35	F	11	0	+	.....	+	Apraxia; blindness	Right and left O., left T.
Case 6	34	M	2	0	+*	Right	+	Right hemianopia	Left T.
Bielschowsky	51	F	8	+	+	Left	0	.....	Right F., T., Ca.

* The epileptiform attacks in these cases were at times jacksonian.

† Ca. = anterior central convolution; Cp. = posterior central convolution; F. = frontal lobe; I. = island of Reil; O. = occipital lobe; P. = parietal lobe; T. = temporal lobe.

portion of the hemisphere" is used here because of its frequent appearance in the literature concerning Lissauer's dementia paralytica; however, there is no physiologic basis for such a division and, as we shall show, it is not applicable to Lissauer's dementia paralytica, because the distribution of the atrophy does not coincide with any such arbitrary division. Microscopically, the cases showed, in addition to the usual signs of dementia paralytica, status spongiosus or pseudolaminar loss of nerve parenchyma in the convolutions, which were macroscopically atrophic, and also a myelin loss in the white matter of the convolutions, which was much more striking than is found in the usual cases of dementia paralytica, but which was generally considered secondary to the extreme destructive process in the cortex. In reviewing the instances in the literature, it was difficult to determine in what percentage status spongiosus was found, as this condition was first accurately described in 1911 by Fischer.[4] The descriptions of the observations in the cases since that date and also in those of Lissauer and Storch[1] and of Alzheimer[2] leave no doubt that such lesions were present in these cases. The distribution of the atrophy (table 1) was remarkably constant. With the exception of the cases of Buder[4] and Bielschowsky,[4] in which the atrophy was chiefly in the frontal lobe and central convolutions, the center of the atrophy appeared to be in the temporal lobe and central convolutions, spreading from these to involve the inferior parietal lobe and the adjacent portions of the occipital lobe. The thalamus and cerebellum were often mentioned as being atrophic, and the atrophy was considered to be secondary to that in the cortex. In none of the cases reported was the degree of inflammatory reaction more marked than in the usual case of dementia paralytica, nor were any noteworthy changes in the blood vessels described. In the fourth case of Alzheimer[2] a small glioma overlay the atrophic area. The views of the various authors as to the pathogenesis of the atrophy will be discussed.

CONSIDERATIONS OF THIS STUDY

We have studied our cases with the purpose of clarifying the following two problems: (1) the nature of the process causing the cortical atrophy and the reasons for its unusual location; (2) the nature and origin of the lesions in the white matter.

In considering the question of the lesions in the cortex, it is known that status spongiosus is most often found in the third and second cortical layers. It is also known that these layers are more vulnerable than the remaining cortical layers. It is necessary to decide, therefore, whether the atrophy is due to the dementia paralytica process alone, or whether it is due to a combination of the dementia paralytica process

with some other factor. With regard to the unusual distribution of the process, it will be necessary to determine whether the atrophic convolutions have any common or peculiar characteristics that distinguish them from the nonaffected areas. With regard to the lesions in the white matter, it is necessary first to determine whether all the lesions are secondary to the degeneration in the cortex, or whether they arise independent of the cortical lesions. If the former is true, these lesions need no further consideration. If, however, they are primary, it is necessary to decide whether they are morphologically the same as the lesions in the cortex, and whether the same factors producing the cortical lesions are responsible for the lesions in the white matter.

REPORT OF CASES

In this section is given a summary of the clinical and pathologic observations in our eight cases. For the sake of brevity, the pathologic observations in the first case will be described somewhat in detail, and in the others only the special findings.

CASE 1.—*A woman, aged 48, of whom a complete history was not obtained, suffered from an illness characterized by severe dementia and by the presence of Argyll Robertson pupils. She had generalized convulsions three days before death. The clinical diagnosis was dementia paralytica. Pathologically, throughout the brain there were the typical changes of dementia paralytica and, in addition, atrophy of the first, second and third temporal, the supramarginal, and the adjacent occipital convolutions of the right hemisphere. The cortex of these convolutions showed either status spongiosus or laminar loss of ganglion cells and loss of myelin. The white matter showed striking loss of myelin, with mobile and fixed "abbau" and proliferation of the protoplasmic and fibrous glia. There was sclerosis of the cornu ammonis.*

History.—M. M., a scrubwoman, aged 48, was brought to the Psychiatrische Klinik, Munich, on July 2, 1930, by the police, who had found her wandering aimlessly through the streets. No relatives were found, and the history, which was very inadequate, was obtained from the patient. At the age of 20, she had had a venereal infection, but did not remember having any treatment. She claimed that she had been able to work up to the time of admission to the clinic. On further questioning, she was found to be disoriented as to time and place. She comprehended questions poorly, was very suggestible in her replies, and showed a marked intellectual defect. The pupils were oval and unequal. They reacted sluggishly on convergence, but did not react to light. The right optic nerve appeared somewhat pale. There was no record of a serologic examination of the blood and cerebrospinal fluid, but these were evidently made, as the clinical diagnosis was dementia paralytica, and the patient was treated accordingly.

Course.—The patient was inoculated with malaria organisms, but the malarial disease was spontaneously cured after one chill and had no effect on the progressive course of the dementia paralytica. Three days before death, the patient had a generalized convulsion. Death resulted on Oct. 19, 1930, from heart failure in the course of an erysipelatous infection superimposed on a bed sore.

Macroscopic Description of the Brain.—The brain was removed, seventeen hours after death, by Dr. H. Spatz, who made the following observations: The

meninges were moderately thickened, especially over the anterior portion of the brain, with obvious atrophy of the underlying convolutions. The ventricles were markedly dilated and showed a striking granular ependymitis. The blood vessels at the base of the brain showed no evidence of arteriosclerosis. On cross-section, there was striking atrophy of the right temporal lobe. The atrophy extended over the entire temporal lobe and also to the opercular portion of the right parietal lobe, and was marked in the supramarginal and angular convolutions. The right lateral ventricle was much larger than the left.

Microscopic Study of the Brain.—Large frontal sections from the right hemisphere were cut, in order to ascertain the extent of the atrophy, and stained with Spielmeyer's myelin sheath stain, cresyl violet, Herxheimer's fat stain and Holzer's glia stain. Smaller sections were stained with Bielschowsky's silver stain, and blocks from all portions of the brain were embedded in celloidin for Nissl's thionine blue stain, the Turnbull blue reaction and Kulschitzky-Wolter's myelin sheath stain.

Throughout the brain the changes characteristic of dementia paralytica were found. The pia and the blood vessels of the brain were moderately infiltrated by plasma cells and lymphocytes, and there was an increase in the glia cells, among which were numerous rod cells. A moderately large quantity of iron pigment was found in the walls of the cortical vessels and in the microglia. All of these changes, though unmistakable, were only of a moderate grade. With the exception of the regions to be described, there were only moderate changes in the nerve parenchyma, with but mild disturbance of the cortical architecture, slight decrease in the number of nerve cells and chronic degenerative changes in some of the remaining cells. There was typical sclerosis of the right cornu ammonis. The large and small vessels of the meninges and cortex did not show any noteworthy changes except for a mild degree of intimal proliferation in the branches of the artery of the sylvian fissure.

In the macroscopically atrophic areas, i. e., the temporal lobe and the inferior parietal lobe, the changes were much more striking. The anterior portion of the temporal lobe was more severely involved than the posterior portion, and the second temporal convolution with the adjoining portions of the first and third convolutions was most markedly atrophic. In these convolutions there was striking loss of nerve tissue, which, although diffuse, was of uneven intensity and gave the appearance of numerous small lesions which through their confluence had produced the large atrophic areas. The tissue destruction was chiefly in the third and second, and occasionally in the sixth and fifth, cortical layers. All components of the cortex were involved, so that in the most atrophic convolutions there were holes of varying size in the cortex, producing the picture known as status spongiosus. In the formation of status spongiosus there are two stages: (1) with the destruction of the nerve tissue, "abbau" products are present and are carried away through the blood stream; (2) there is a proliferation of the glia, which in the very acute stages are chiefly protoplasmic astrocytes; these are later replaced by fibrous astrocytes.

In this case, very little of "abbau" products was found in the atrophic areas. There was only a small amount of neutral fat in the perivascular spaces. There was, on the other hand, marked marginal gliosis, and numerous fibrous and protoplasmic astrocytes were found in the atrophic cortex. In the postcentral convolution, which was not as strikingly atrophic, a moderate amount of neutral fat was found in fixed and mobile glia cells.

The remaining ganglion cells of the atrophic convolutions showed various degenerative changes. The large cells of the third layer showed the chronic

changes of Nissl, and many of the small cells of the fifth and sixth layers showed a remarkable type of reaction, which has been described in the German literature as "Zellblähungen."[5] In the thionine blue stains, the cells appeared swollen and rounded, the Nissl granules had disappeared, the protoplasm stained a faint pink, and the nucleus was crowded to the edge of the cell (fig. 1). This type of cell change is very similar to that found in the so-called axonal reaction. These cells could possibly be confused with "gemästete" glia, but unmistakable transitional forms between normal ganglion cells and the swollen cells could be found, and further stages of degeneration in which the cell body had partially disappeared. With Bielschowsky stains, the cells were homogeneously impregnated, with a somewhat dusty appearance. The cells were found only in the deeper cortical layers of those convolutions that showed status spongiosus in the third and second layers.

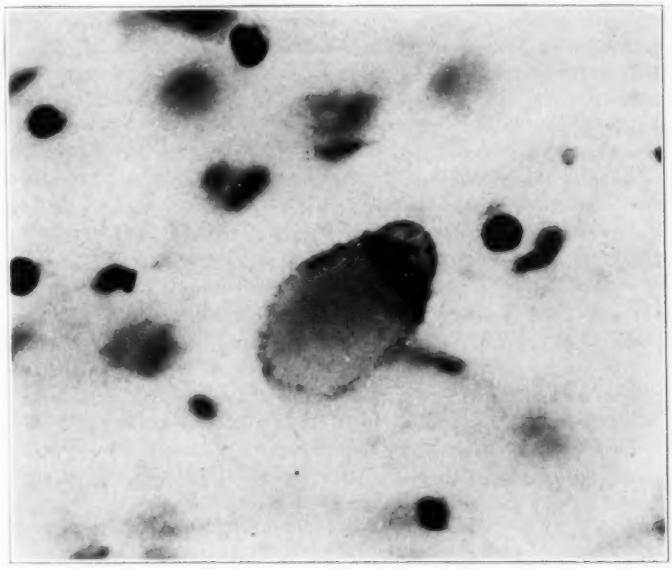


Fig. 1 (case 3).—A ganglion cell from the fifth layer of the cortex of the inferior parietal lobe showing the so-called "Zellblähungen."

Since it is well known that in status spongiosus the myelin sheaths and nerve fibers are also involved, the changes found in these structures will not be discussed in detail here, except to state that, in addition to marked diffuse loss of myelin in the most atrophic areas, circumscribed lesions similar to the "Markfleckenbildungen" of Borda,[6] Fischer[7] and Spielmeyer[8] were found in the less atrophic areas.

Another peculiarity of the atrophic areas was the form in which the iron pigment was found. In the status spongiosus, iron pigment was found only in a small quantity, and this was in compound granular cells with practically no pigment in the walls of blood vessels.

As previously stated, the status spongiosus was not of equal intensity in the various convolutions. It was most marked in the anterior portion of the second,

5. v. Braunmühl, A.: Picksche Krankheit; Die Anatomie der Psychosen, in Bumke: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

and the adjacent portions of the first and third temporal convolutions. It was found also in the remaining portion of the first and third temporal convolutions and in the supramarginal, angular and postcentral convolutions.

In addition to the changes described in the cortex, there were lesions in the white matter. There was marked loss of myelin in the white matter of all the convolutions showing status spongiosus. These lesions were found chiefly in two locations: (1) at the apex of the convolutions (as shown in fig. 12) and (2) deep in the white matter. The latter lesions were more localized and were generally found around blood vessels. In some of the lesions, neutral fat could be found in compound granular cells and in others only in the fixed glia. With the Holzer stains, a gliosis was found that corresponded in degree to the amount of myelin loss shown with the Spielmeyer stains. With Nissl stains, the white matter of the atrophic convolutions appeared rich in nuclei, and in the parietal region, where the gliosis was not marked, these were protoplasmic glia.

CASE 2.—*In a housewife, aged 63, an illness of six years' duration was characterized by mental deterioration, repeated transient attacks of amblyopia, transient right hemiplegia, convulsive attacks on the right half of the body and aphasia. The serologic tests were typical of dementia paralytica. The usual changes of dementia paralytica were found throughout the brain, and, in addition, macroscopic atrophy and an extreme degree of status spongiosus in the pole of the left temporal lobe and to a less marked degree in the rear half of the temporal lobe, in the supramarginal and angular convolutions and in the adjacent portion of the postcentral and occipital convolutions. There were marked loss of myelin in the white matter of the atrophic areas and sclerosis of the cornu ammonis on the left side. Mild arteriosclerotic changes were present in the large blood vessels of the sylvian fissure.*

History.—M. I., a married housewife, aged 60, who was admitted to the Psychiatrische Klinik, Munich, on Nov. 18, 1924, for three years previously had had frequent transient spells of amblyopia in one eye. Early in June, 1924, she had a sudden disturbance of speech that lasted only a few days. In the latter part of the same month, she became suddenly paralyzed on the right side and aphasic. The paralysis cleared up in fourteen days, but the speech disturbance persisted.

Examination.—On admission, the patient was euphoric and talkative, sometimes incoherent, and showed evidences of marked mental deterioration. The pupils were miotic, and reacted in convergence, but very sluggishly to light. There was paralysis of the right half of the face, of the central type, and the right arm was ataxic. The knee and ankle jerks were absent. There was a Babinski reflex on the right side. The use and understanding of words were limited, but there appeared to be an uncontrollable urge toward talking. The Wassermann reaction of the blood was 4 plus. The cerebrospinal fluid showed 6 cells per cubic millimeter; the result of the Pandy test was 3 plus, the colloidal gold reaction was 5443321000, and the Wassermann reaction was 4 plus in a concentration of 0.2 cc.

Course.—The patient improved and was released on Jan. 10, 1925, but was readmitted on June 22, 1925. During the interval, she had been able to do work

---

6. Borda, J. T.: Paralysie générale progressive; contribution à l'étude de son anatomie et de son histologie pathologique, Rev. Soc. méd. argent. **13**:377, 1905.

7. Fischer, O.: Ueber einem eigenartigen Markfaserschwund in der Hirnrinde bei Paralyse, Wien. klin. Wchnschr., 1906, no. 22.

8. Spielmeyer, W.: Ueber einige anatomische Aehnlichkeiten zwischen progressiver Paralyse und multipler Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **1**:660, 1910.

around the house, but still had difficulty in using words. She had also had transient spells of paralysis without loss of consciousness. The neurologic and serologic conditions were the same as at the previous admission. She was treated with mercury and improved enough to be released on July 31, 1925. She had another partial remission until July 13, 1926, when it was necessary for her to be admitted again to the hospital. In the interval she had had spells of short duration characterized by convulsive movements in the right arm. Also a few months before admission, there was a sudden transient increase of the speech disturbance. On the third admission, the patient showed marked dementia, and the disturbance of speech was more evident. The ability to construct sentences was lost, and there was a marked paraphasia. The cerebrospinal fluid showed, as on the previous two admissions, a 4 plus Wassermann reaction in a concentration of 0.2 cc. and a colloidal gold curve of 5443210000. The course was progressively downward, and the patient died on May 6, 1927, on the seventh day of an attack of facial erysipelas.

Macroscopic Description of the Brain.—The brain was sectioned twelve hours after death by Dr. H. Spatz. The dûra was adherent to the skull, and on its undersurface was brownish and covered in places by a pseudomembrane. There was a moderate external hydrocephalus. The meninges were moderately thickened and showed small fresh hemorrhages. The blood vessels at the base of the brain were slightly thickened. The entire brain appeared atrophic, but the atrophy was particularly striking on the left side, especially at the pole of the temporal lobe, the posterior portion of the temporal lobe and the supramarginal convolutions, whereas the remainder of the parietal lobe was spared except for the postcentral convolution, which was moderately atrophic. On palpation, the left temporal lobe felt like a flabby sack. The extent of the atrophy on the left side could be clearly seen in frontal sections of the brain. The second and third temporal, the fusiform, the hippocampal and the supramarginal convolutions were most markedly atrophic. The first temporal, the postcentral and the anterior occipital convolutions were also atrophic, but not as markedly as those mentioned. The left ventricle was greatly dilated, especially in its posterior horn, and the mass of the white matter of the left hemisphere, particularly in the temporal lobe, was markedly reduced. The left thalamus appeared smaller than the right. The macroscopic iron reaction was 4 plus.

Microscopic Study of the Brain.—The same stains were used in this as in the previous case, and in addition Klarfeld's modification of Achucarro's silver stain for blood vessels. Large frontal sections of the left hemisphere were embedded in celloidin for Nissl's cell stain and also for Kulschitzky-Wolter's myelin sheath stain.

The typical changes of dementia paralytica were found everywhere in the cortex and in the basal ganglia; i. e., the meninges and cortical blood vessels were moderately infiltrated by lymphocytes and plasma cells; there was a proliferation of the glia cells with many rod cells; there was a moderate quantity of iron pigment in the microglia and in the walls of the blood vessels, and there were mild degenerative changes in the nerve parenchyma. The larger branches of the artery of the sylvian fissure showed very slight arteriosclerotic changes. In the frontal lobe, two small "Erbleichungsherde" were found in the sixth layer. There was typical sclerosis of the left cornu ammonis.

In contrast to the changes in the relatively well preserved areas were those found in the macroscopically atrophic convolutions. With the Nissl thionine stains, there was extreme status spongiosus of the entire cortex at the pole of the left temporal lobe. The holes in the tissue were very large, and scarcely a ganglion cell was found. In the posterior portion of the temporal lobe, the fusiform, hippocampal, supramarginal, angular, posterior portion of the postcentral, and anterior occipital

convolutions, status spongiosus was also found, but in a milder form. There were holes in the tissue in the second and third layers, and occasionally in the fifth and sixth layers. Most of the remaining ganglion cells showed the typical chronic changes described by Nissl. A few cells were found in the fifth and sixth layers of the atrophic convolutions which showed the "Zellblähungen" previously described. Myelin stains showed extreme loss of the myelin in the atrophic cortex, which occasionally extended into the subcortical white matter. The lesions in the cortex appeared to be fairly old, as no neutral fat was found with the Herxheimer stain, except in the postcentral convolution and at the junction of the upper and lower halves of the parietal convolutions. Holzer glia stains showed fibrous gliosis in the first layer and numerous fibrous astrocytes scattered throughout the atrophic cortex. Iron stains of the atrophic regions showed only a slight amount of iron pigment, and this was mostly in compound granular cells, with only a small amount in fixed glia cells or in the walls of blood vessels.

In all of the convolutions mentioned there was striking loss of myelin in the white matter. The myelin loss in the white matter can be divided into three types: (1) localized loss in the subcortical white matter, which was apparently a continuation of the lesions in the cortex; (2) localized accentuations of the diffuse loss of myelin in the deeper portion of the white matter underlying the atrophic cortex; (3) loss of myelin in the tapetum and precuneus, independent of the cortical atrophy. With the Nissl stains, the white matter in the regions mentioned appeared rich in glia cells, which was partially accounted for by the pressing together of the glia nuclei resulting from the shrinking of the convolutions. With Holzer glia stains, there was a moderately thick gliosis in the areas corresponding to those showing myelin loss with the Spielmeyer stains. Evidence of fresh "abbau" was not found in these lesions, except in the postcentral convolution and in the area between the upper and lower portions of the parietal lobe. Figure 2 presents a frontal section of the left hemisphere in the region between the parietal and occipital lobes, which shows the enormous dilatation of the left ventricle and the striking loss of myelin in the white matter. The thalamus on the left side, which appeared macroscopically small, showed diffuse loss of ganglion cells and myelin sheaths.

Case 3.—*An errand boy, aged 23, suffered from an illness of eleven years' duration, characterized by progressive dementia, articulatory speech disturbance, jacksonian and generalized convulsions, and left hemiplegia. The serologic tests were typical of dementia paralytica. The usual dementia paralytica changes were found throughout the brain, and in addition there were macroscopic atrophy, status spongiosus of the cortex and myelin loss in the white matter of the anterior and lower portion of the frontal lobe, the temporal lobe, the supramarginal, the angular, the postcentral, the opercular portion of the precentral and the anterior occipital convolutions. There was atrophy of both thalami, as well as degeneration of the left pyramidal tract in the spinal cord.*

History.—J. S., an errand boy, aged 21, was admitted to the Psychiatrische Klinik, Munich, on June 16, 1926. His mental and physical development had been considered normal until he reached the age of 12 years; after this age his physical development became markedly retarded, and he was also unable to advance further in school. He was inattentive and related fantastic stories. After quitting school, he was unable to do any productive work. He was given a position in his uncle's barrel factory, but could be used only as an errand boy. Several weeks before admission there was a sudden change in the condition; he became confused, inattentive, talked incoherently and had spontaneous outbursts of laughing and crying.

Examination.—The patient was markedly undernourished and underdeveloped, with undeveloped primary and secondary sex characteristics. The pupils did not react to light or in convergence. All the deep reflexes were exaggerated, except the ankle jerks, which were diminished. The speech showed an articulatory defect. The patient was imperfectly oriented; his memory was faulty and his judgment poor. The Wassermann reaction of the blood was 4 plus. The cerebrospinal fluid contained 21 cells per cubic millimeter; the Nonne test was positive, and the Wassermann reaction was 4 plus.

Fig. 2 (case 2).—A frontal section in the region between the occipital and parietal lobes showing striking loss of myelin; Kulschitzky stain.

Course.—The patient was inoculated with the organisms of malaria on five occasions, without any febrile reaction. He showed marked improvement, however, gaining 4 cm. in height and considerable weight. He became more alert and busied himself with small duties around the hospital. He was released on Oct. 25, 1926, and readmitted on June 31, 1927. In the interval, he had been able to do a little work, but was not dependable. Two days before admission, there was sudden paralysis of the left arm, and he was unable to talk. Examination on readmission showed, in addition to the conditions previously recorded, rhythmic twitchings of the muscles of the left half of the face, tongue and palate and of the platysmal muscle. There were weakness of the left arm and clonic movements of the left

thumb and index finger. The speech was scarcely understandable owing to an extreme articulatory defect. The paralysis and disturbance of the speech improved, and the patient was released on Aug. 5, 1927. He continued to make progress at home until Jan. 17, 1928, when he had a generalized convulsion and was unconscious for five minutes. On the following day, he had six convulsions, and he was brought to the hospital on Jan. 19, 1928. On admission, he was quiet and did not speak; there was left hemiplegia; the deep reflexes were increased on both sides, and there was a Babinski reflex on the left. The course was progressively downward, with numerous epileptic convulsions, many of which were confined to the left half of the body and were not accompanied by loss of consciousness. The patient died on Nov. 16, 1928.

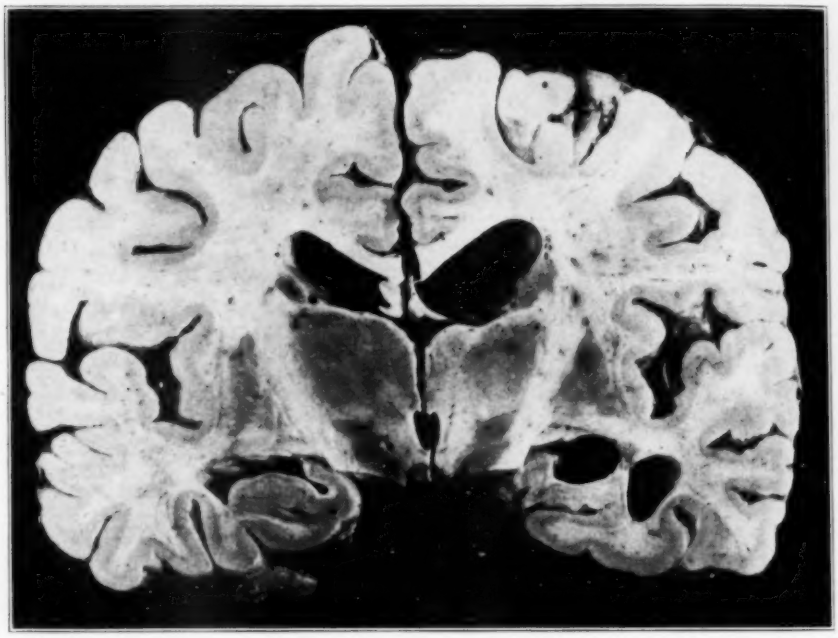


Fig. 3 (case 3).—A frontal section in the region of the central convolutions showing atrophy of the right hemisphere. The most striking atrophy is seen in the hippocampus, T_3, T_2, the lower half of T_1 and the postcentral convolution. Note the dilated ventricles on the right side. Compare with figure 4.

Macroscopic Description of the Brain.—The brain was sectioned thirteen hours post mortem by Dr. H. Spatz. The meninges were thickened over the convexity, and there was an increase in the amount of the subarachnoid fluid. The right hemisphere appeared much smaller than the left. In the left hemisphere the atrophy was moderate, involving only the frontal lobe. The atrophy on the right side was marked, and only certain convolutions were especially involved. The most remarkable atrophy was in the parietal portion of the postcentral convolution, the supramarginal, angular and first temporal convolutions, the entire temporal pole, the insula, the opercular and orbital regions of the frontal lobe, and the frontal pole (fig. 3). The right lateral ventricle was greatly dilated. In the atrophic convolu-

tions, the cortex was reduced to a narrow ribbon, and the width of white matter was also diminished. There were moderately marked ependymal granulations in the walls of the ventricles.

Microscopic Study of the Brain.—Throughout the brain, with the exception of the posterior portions of the occipital lobes, the typical changes of dementia paralytica were found. The meninges and the cerebral blood vessels were moderately infiltrated by lymphocytes and plasma cells. This infiltration was especially marked in the cornu ammonis and in the striatum. The large blood vessels of the brain were imbedded in celloidin and stained, but no noteworthy changes were

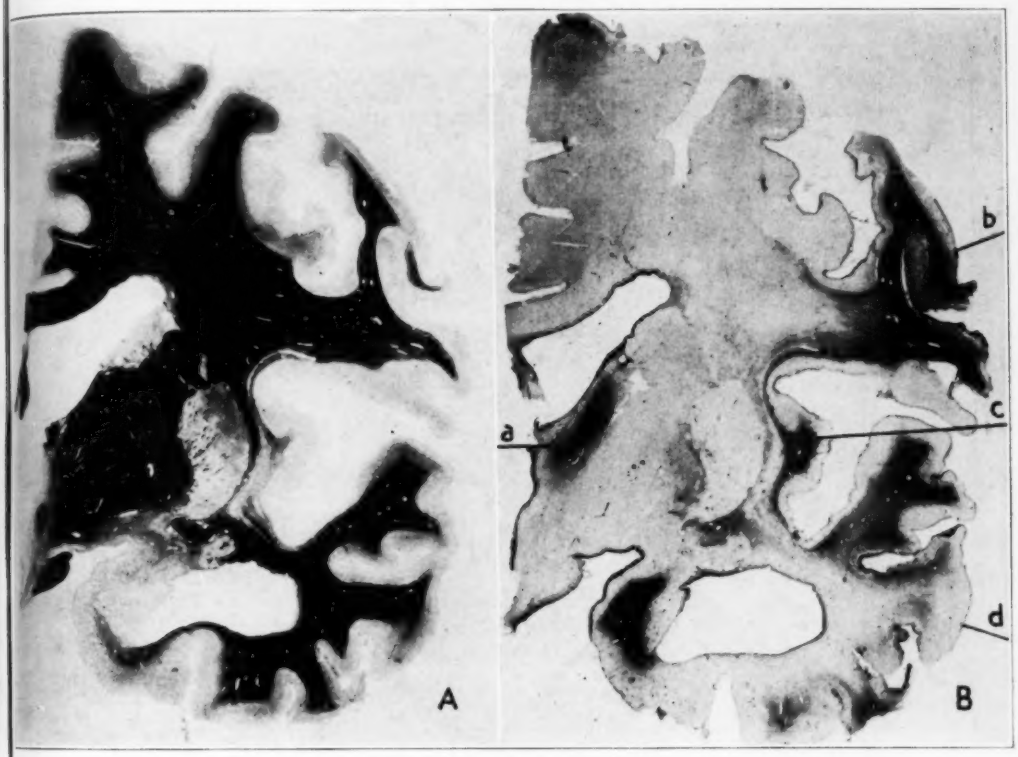


Fig. 4 (case 3).—Corresponding frontal sections of the right hemisphere showing the myelin loss and the degree of gliosis in the postcentral convolution and in the temporal lobe. *A* shows the Spielmeyer stain, the negative picture; *B*, the Holzer stain, the positive picture: (*a*) anterior nucleus of the thalamus; (*b*) postcentral convolution; (*c*) capsula extrema, and (*d*) temporal lobe. Note the myelin loss and gliosis in the capsula extrema and externa and in the anterior nucleus of the thalamus. Compare with figure 3.

found. Iron pigment was found in moderate amounts in the walls of the blood vessels and in the microglia of the left hemisphere.

The atrophic convolutions on the right side were: the most anterior frontal convolution, the gyri orbitalis, the inferior frontal convolution, the insula, the entire temporal lobe, including the gyrus fusiformis and the hippocampus, the

supramarginal and angular gyri, the adjacent portions of the occipital lobe and the postcentral convolution, and the opercular portion of the precentral convolution.

In the more atrophic regions enumerated, there was outspoken status spongiosus, chiefly in the second, third, fifth and sixth cortical layers. In some places this was so marked that only the fourth layer remained. In these regions, as in the former cases, many of the small ganglion cells of the sixth layer showed swelling, displacement of the nucleus and pale staining of the cell protoplasm (Zellblähungen). No iron pigment was found in the atrophic areas. With Herxheimer's stain, no neutral fat was found in these regions, except in the areas between the more atrophic and the better preserved cortex, where numerous compound granular cells laden with neutral fat were seen.

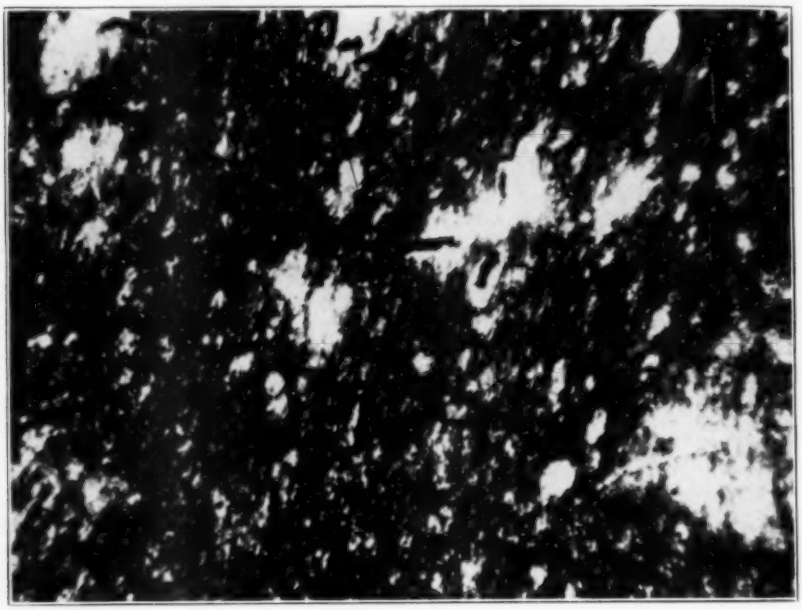


Fig. 5 (case 3).—A section from the inferior parietal lobe showing the status spongiosus-like appearance in the white matter; Spielmeyer stain.

In the white matter of the atrophic convolutions there was marked loss of myelin, and also deep in the subcortical white matter there were localized areas in which there was loss of myelin (fig. 4). These areas did not seem to have any relation to the blood vessels. In these areas, Herxheimer's stain showed a large number of compound granular cells loaded with neutral fat. With this stain, the circumscribed nature of the lesions in the white matter was apparent. With the glia fiber stains, the positive picture of the myelin stains was seen, with a marked gliosis in the regions where the myelin loss was most evident. The degree of gliosis was greater than was expected. In the white matter of the supramarginalis-angularis region, localized lesions were present in which all of the tissue was destroyed, resulting in small holes, giving an appearance similar to status spongiosus (fig. 5).

Both thalami were very small, especially the right, and the cell and fiber loss was most marked in the anterior nucleus. In the medulla there was marked degeneration of the right pyramidal tract, which could also be seen in the sections from the spinal cord.

CASE 4.—*A boy, aged 16, presented congenital syphilis and mental retardation. The neurologic and serologic tests were typical of dementia paralytica, and the clinical picture was characterized by progressive dementia, numerous epileptic convulsions and contractures of the extremities. The patient died in a marasmic state after six years in the hospital. Only the right half of the brain was studied; this showed the usual signs of dementia paralytica and, in addition, macroscopic atrophy, status spongiosus in the cortex, diffuse and localized myelin loss in the white matter of the temporal, parietal and occipital lobes and the island of Reil, fresh hemorrhages in the occipital lobe and the island of Reil (the result of sinus thrombosis), sclerosis of the cornu ammonis and lobular sclerosis in the cerebellum.*

History.—E. M., a boy, aged 10, who was admitted to the Psychiatrische Klinik, Munich, on Feb. 21, 1922, had attended school for five years, but had been unable to pass the first grade. His behavior had always been good, but he would cry on the least provocation and was very dependent on his mother.

Examination.—The teeth were hutchinsonian; the pupils were irregular and unequal and reacted poorly to light; the deep reflexes were increased, and there was an articulatory disturbance of speech. The patient was quiet, easily suggestible and showed a marked lability of mood. His mental age according to the Binet-Simon test was 6. The Wassermann reaction of the blood was strongly positive. The cerebrospinal fluid contained 18 cells per cubic millimeter; the Nonne-Appelt reaction was positive, and the Wassermann reaction was 4 plus in concentration of 0.2 cc.

Course.—The patient was inoculated with the organisms of malaria, and given inunctions with mercury. He was released to his parents on June 30, 1922. On Nov. 13, 1922, he was admitted to the Heil und Pflegeanstalt, Haar, where his condition was the same as previously recorded. There was little change in his condition until December, 1926, when he had the first epileptic convulsions. The course then was progressively downward until death on April 1, 1928, with convulsions almost daily for one year of this period. The record was not satisfactory; nothing was stated in regard to the neurologic and physical status of the patient, except that contractures of the extremities developed which were not described further.

Necropsy.—Dr. K. Neubürger reported an old verrucous endocarditis and old tuberculosis of the lungs and of the hilar lymph nodes. There were thrombosis of all the venous sinuses of the brain, atrophy of the cortex and fresh hemorrhages into the right occipital lobe.

Macroscopic Description of the Brain (Hardened in Formaldehyde).—Only the right hemisphere, the brain-stem and the cerebellum were at hand when this study was made, but since the type and the distribution of the changes were exactly similar to those in the other cases they are included in this study. The meninges were thickened, particularly over the convexity. There was moderate atrophy of the frontal convolutions, but the most striking atrophy was in the temporal lobe, the island of Reil, the lower parietal lobe and the occipital lobe. Near the tip of the occipital lobe was a fairly large, fresh extravasation of blood into the cortex. On section of the brain, the right ventricle was considerably dilated, particularly in the temporal and occipital horns. The second temporal and the occipital convolutions appeared most atrophic. There was a fine granular ependymitis of the floor

of the fourth ventricle. An accurate description of the cerebellum was not possible from the portions at hand. The thalamus appeared small.

Microscopic Study of the Brain.—Sections were taken from various portions of the right hemisphere, brain-stem and cerebellum and were stained according to the previously mentioned methods.

All of the sections showed the changes usually described as typical of dementia paralytica. The inflammatory reaction was mild, with only a moderate number of plasma cells and lymphocytes in the meninges and in the perivascular spaces. The degenerative changes, on the other hand, were striking. In the frontal lobe and central convolutions, where the atrophy was not so striking macroscopically, there were numerous ganglion cells showing the chronic cell changes of Nissl, and there

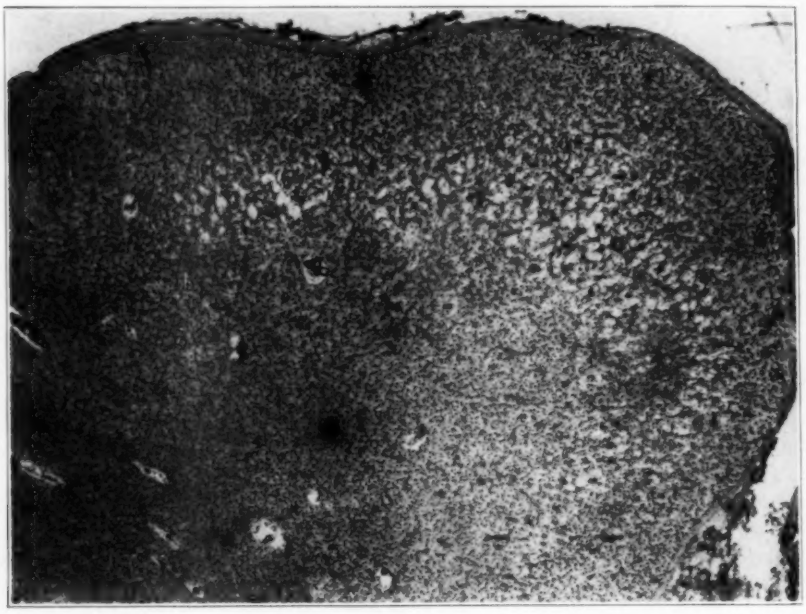


Fig. 6 (case 4).—Hematoxylin and eosin-stained section from the temporal pole showing the spongy appearance of the cortex—status spongiosus.

was a strikingly large number of rod cells. Myelin sheath stains of these regions showed only a diffuse loss of myelin in the cortex and several of the small localized lesions commonly found in dementia paralytica.

Sections from the macroscopically atrophic areas showed either outspoken status spongiosus in the second and third layers, or laminar loss of cells in these areas. Status spongiosus was most marked at the pole of the temporal lobe, in the second temporal convolution and in the anterior occipital convolutions (figs. 6 and 7). Many of the remaining ganglion cells showed ischemic and chronic changes. Nissl and Holzer stains showed numerous fibrous glia throughout the cortex of these regions, particularly in the first layer of the cortex. With myelin sheath stains there was complete loss of myelin in the cortex of the convolutions showing status spongiosus and diffuse loss in the less atrophic areas. In addition to these changes, there were in one small portion of the occipital lobe and the island of Reil fresh

hemorrhagic areas. These lesions were made up of numerous small extravasations, in the middle of many of which a blood vessel could be seen. Surrounding these areas there was a zone of reacting glia cells, chiefly of the gitter type, and a beginning proliferation of the blood vessels. In the thalamus there was apparent loss of ganglion cells, and many of the remaimng ganglion cells showed severe degenerative changes. Sections from the cerebellum showed lobular sclerosis throughout and also several glia "Strauchwerk." There was typical sclerosis of the cornu ammonis. Iron stains showed large quantities of iron pigment throughout the cortex in the microglia and in the walls of the blood vessels. In the status spongiosus, however, there was little iron, and this was chiefly in compound granular cells. Herxheimer's stains of the cortex showed only a small quantity of fat in the perivascular spaces.

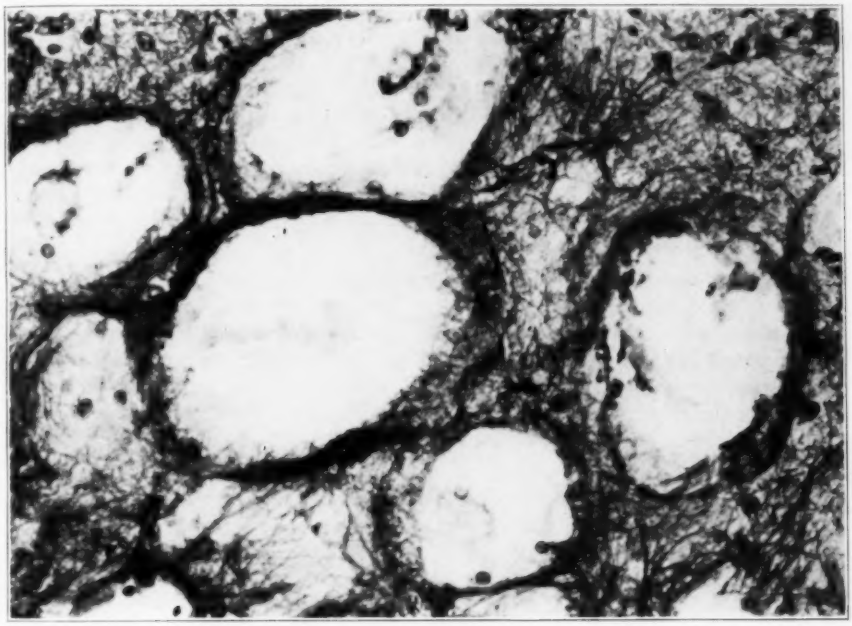


Fig. 7 (case 4).—A highly magnified picture of the status spongiosus in the cortex as seen with Holzer's stain for glia fibers. The glia network is thickest around the edge of the holes. The section is from the temporal pole.

In the white matter of all the convolutions where status spongiosus was found, and especially at the anterior pole of the temporal lobe, there was marked diffuse loss of myelin. In these regions there was moderate gliosis as shown by the Holzer stain. The lesions in the white matter were apparently old, as no neutral fat was found in them, except for a small amount in the perivascular spaces. Myelin sheath stains of sections from the medulla did not show loss of myelin in the pyramidal tract.

CASE 5.—*A former soldier and salesman, aged 47, had a mental disturbance extending over a period of fourteen years. Neurologic and serologic examinations showed atypical dementia paralytica. There was an aphasia-like disturbance of speech, and numerous convulsions were noted during the last two years of life,*

which were at times confined to the left side. The patient died in status epilepticus. The usual changes of dementia paralytica were found throughout the brain and, in addition, macroscopic atrophy, status spongiosus and extensive myelin loss in the temporal lobes, and the supramarginal, angular and adjacent occipital convolutions on both sides, more marked on the right side. There was sclerosis of the right cornu ammonis.

History.—F. T., a salesman, aged 40, was brought to the Psychiatrische Klinik, Munich, on Aug. 18, 1923, by the police on account of contracting many debts and refusing to pay them. In June, 1916, while in the army, he had several fainting spells, and he received a slight wound in July, 1916. He was under observation in the military hospital at intervals on account of mental troubles and alleged inability for military service. He was released from service in 1917. After release, he was treated at various hospitals for gonorrhea, syphilis and mental disturbances, and was admitted to the Heil und Pflegeanstalt, Bayreuth, on Jan. 12, 1921, having been transferred there from a neighboring general hospital. He showed mental deterioration and complained continually that his condition was due to service in the army. He was transferred to the Heil und Pflegeanstalt, Eglfing, on April 26, 1921, where he remained until December, 1921, during which time he was disoriented, heard voices, and on occasions refused all nourishment. He was released to his family, but returned voluntarily on Feb. 17, 1923, in a dazed, anxious condition. He remained only until March 9, 1923, however, and after release was able to work for a short time as a salesman.

Examination.—On admission to the Psychiatrische Klinik, Munich, he was quiet, oriented and friendly. His speech was automatic and showed echopraxia. The pupils were dilated and reacted poorly to light. The tendon reflexes were exaggerated. The Wassermann reaction of the blood, which on previous occasions had varied from 4 plus to negative, was 1 plus. A lumbar puncture, which the patient had previously refused to allow, showed 73 cells per cubic millimeter, and the Wassermann reaction was 3 plus.

Course.—He was transferred to the Heil und Pflegeanstalt, Haar, on Sept. 27, 1923, with a diagnosis of dementia paralytica, and remained there until he died, on Jan. 18, 1930. The course was progressively downward, with increase in mental loss. On May 12, 1928, the first epileptic convulsions were noted, with a tendency for the convulsions to involve the left side only; these continued to occur until death. The Wassermann reaction of the blood was strongly positive, but no further lumbar punctures were attempted. The patient's speech was unintelligible. He died on Jan. 18, 1930, in status epilepticus. He was treated at various intervals during the illness with arsphenamine and mercury.

Macroscopic Description of the Brain (Hardened in Formaldehyde).—Externally, the right half of the brain appeared considerably smaller than the left, particularly in the temporal and inferior parietal lobes. Both lateral ventricles were dilated, but the descending horn on the right side was considerably larger than that on the left. The right frontal lobe was also obviously smaller than the left. On section of the brain, the extent of the atrophy was more clearly seen. It was most striking on the right side in the first and second temporal convolutions and to a less extent in the third. The gyrus fusiformis and the cornu ammonis were also definitely atrophic. The atrophy was also obvious in the supramarginal and angular gyri. The floor of the fourth ventricle showed mild ependymitis. The blood vessels at the base of the brain appeared normal. The meninges were moderately thickened over the convexity. The macroscopic iron reaction was positive according to the records of the test that was made at the necropsy.

Microscopic Study of the Brain.—In spite of the macroscopically more marked atrophy of the right side, it must be noted that the changes on both sides were qualitatively similar, and that they were only more intensive on the right side. The typical changes of dementia paralytica were found everywhere: mild infiltration of the meninges and the cortical blood vessels by lymphocytes and plasma cells,

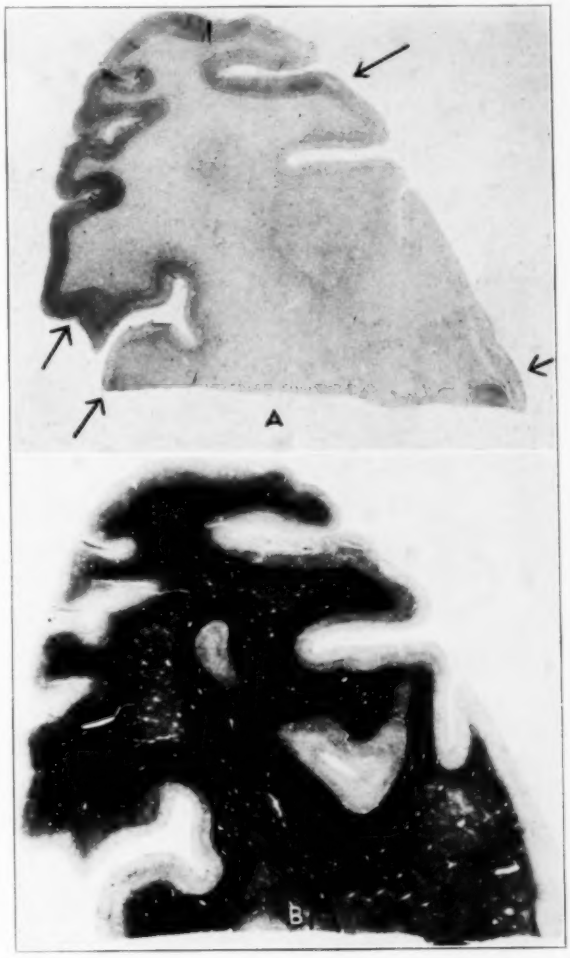


Fig. 8 (case 5).—Horizontal sections from the right occipital lobe and the adjoining portion of the parietal lobe showing status spongiosus in the cortex and myelin loss in the cortex and white matter. The myelin loss in the white matter is seen also in convolutions with fairly well preserved cortex. The lesions were relatively fresh, as was shown by the presence of a large amount of neutral fat in sections stained with Herxheimer's stain and the absence of a marked gliosis in those stained with Holzer's stain. *A* shows the staining with cresyl violet; *B*, that with Spielmeyer's stain. The area between the arrows indicates the portions of the cortex that showed status spongiosus.

proliferation of the glia, many rod cells, a markedly positive iron reaction and degenerative changes in the parenchyma. The larger vessels of the pia showed no proliferative or degenerative changes in their walls. The cortical architecture was everywhere markedly disturbed, and the layers were scarcely recognizable. Many of the ganglion cells showed marked changes that were frequently of the so-called

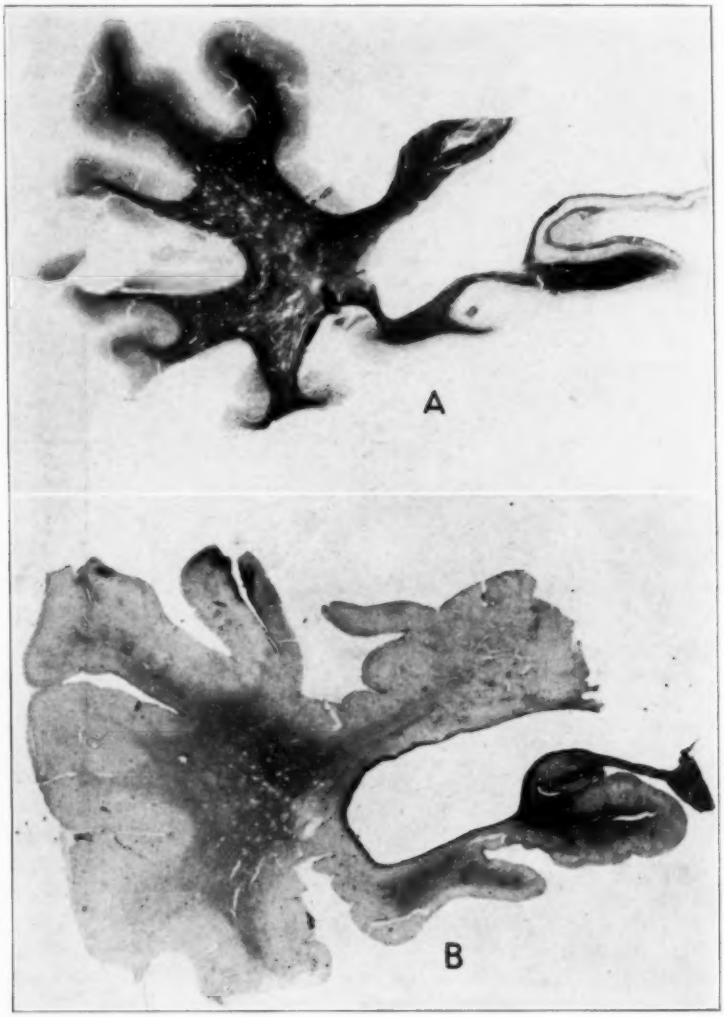


Fig. 9 (case 5).—*A* pictures a section of the right temporal lobe showing myelin loss, Spielmeyer's stain; *B*, a corresponding section showing the degree of gliosis, Holzer's stain. Note the glial reaction in the sclerotic cornu ammonis.

ischemic type. In several places a large amount of neutral fat was found, which was taken up by the fixed glia (frontal lobes). In the precentral convolution, the beginning changes of the axonal reaction were found in the Betz cells. (The best preserved cortex was in the region of the calcarine fissure.)

In the postcentral, two lower temporal, fusiform, supramarginal, angular and adjacent occipital convolutions, status spongiosus was found. In the temporal and postcentral convolutions status spongiosus was marked. In the latter, it appeared as sharply circumscribed streaks involving chiefly the second and third layers, and in places the fifth and sixth layers, in unequal intensity. The supramarginal and angular convolutions were involved even more intensively than the convolutions mentioned. Many of the ganglion cells still present in the atrophic areas showed the so-called ischemic changes, and some of the large cells of the third layer showed the chronic cell changes of Nissl. Many of the small cells of the fifth and sixth layers showed the peculiar changes previously described (Zellblähungen). Neutral fat was found only in certain places and was chiefly in compound granular cells.

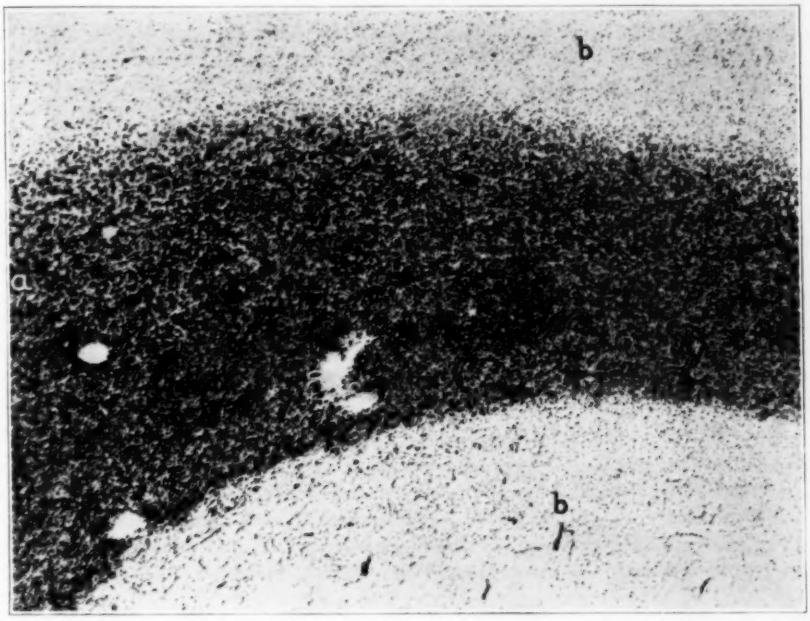


Fig. 10 (case 5).—A section of one of the anterior occipital convolutions of the left hemisphere showing an enormous quantity of neutral fat (black in the picture) in the white matter (*a*) and a moderate amount in the cortex (*b*); Herxheimer stain.

The gliosis on the surface of the cortex was very thick, and in the whole cross-section of the cortex were numerous large fibrous astrocytes. In the atrophic areas there was extreme loss of myelin in the cortex. Iron pigment was found in compound granular cells in the status spongiosus. In the cornu ammonis and hippocampus no status spongiosus was found, but on the right side there was typical sclerosis of the cornu ammonis.

The white matter of the atrophic convolutions was involved to a marked degree. Wherever there was status spongiosus in the cortex, there was in the white matter marked destruction of the myelin. This was particularly true for the temporal and supramarginal-angular regions and for the occipital lobe. In the latter, the area of

myelin loss involved a much greater portion of the lobe than the status spongiosus. Figures 8 and 9 show the degree of myelin loss in the occipital and temporal lobes, respectively.

Wherever status spongiosus was found in the cortex, there were two sites of predilection for the loss of myelin in the white matter, namely, at the apex of the convolution (fig. 10) and in the depth of the white matter. The subcortical white matter at the base of the convolutions was fairly well preserved. With myelin stains, it was readily seen that the areas of myelin loss were not diffusely or evenly distributed, but sharply localized. Herxheimer's stains showed an enormous amount of neutral fat in the areas of myelin loss. The amount of fat was much greater than was expected from the degree of myelin loss as shown by the myelin sheath stains. Figure 10 shows the amount of neutral fat in one of the anterior occipital convolutions. In the deeper part of the white matter, the neutral fat was not diffusely distributed over the involved regions, but was usually found in localized areas corresponding to those showing myelin loss with the Spielmeyer stain. With the Holzer stain for glia fibers, there were numerous glia fibers and large fibrous astrocytes, but there was not a thick fibrous network. The Nissl stains showed many protoplasmic glia cells (frequently in the form of "gemästete glia"), which was consistent with the absence of a thick fibrous network in the Holzer preparations. The degree of the axis cylinder loss as shown by Bielschowsky stains was difficult to determine. Many of the preserved axis cylinders showed typical early degenerative changes. In this connection it should be stated that the myelin loss was not confined to any definite fiber tracts, but extended beyond the borders of such systems. However, the external sagittal fibers were better preserved than the remainder. Inflammatory changes in the blood vessels of the white matter were found only in one portion of the occipital lobe. Here the vessels were infiltrated by lymphocytes and plasma cells, and in the vicinity there was extremely marked proliferation of the protoplasmic glia.

CASE 6.—*A soldier, aged 54 years at death, suffered from an illness of thirteen years' duration which was characterized by progressive dementia, apoplectiform and epileptiform seizures and left hemiplegia. The neurologic and serologic tests were typical of dementia paralytica. Pathologically, there were the usual changes of dementia paralytica throughout the brain and macroscopic atrophy of the posterior portion of the frontal lobe and of the temporal and inferior parietal lobes on the right side. Microscopically, these regions showed pseudolaminar loss of cells or mild status spongiosus and a loss of myelin in the white matter. There were sclerosis of the right cornu ammonis and degeneration of the right pyramidal tract in the medulla.*

History.—W. K., a soldier, aged 41, was admitted to the Psychiatrische Klinik, Munich, on Aug. 27, 1918. He was a guard in the army prison when two Russian prisoners escaped. After this, there was a change in his mood and behavior.

Examination.—Pupillary disturbances, exaggeration of the deep reflexes, articulatory disturbance of speech and a writing defect were found. The Wassermann reactions of the blood and cerebrospinal fluid were strongly positive.

Course.—A diagnosis of dementia paralytica was made, and the patient was released on Dec. 8, 1918, to his family. He was readmitted on Sept. 29, 1922, when he was brought in by the police. In the interval, the patient had been able to work in the street-cleaning department, but was not efficient even at this low grade of work. On this admission, he was euphoric and evidently had deteriorated mentally. He did not understand why he was brought to the hospital. The physical

signs were the same as those previously recorded, and the Wassermann reactions of the blood and cerebrospinal fluid were again strongly positive. The cerebrospinal fluid contained 80 cells per cubic millimeter. On Oct. 22, 1922, the patient was transferred to the Heil und Pflegeanstalt, Gabersee, where he remained until death. On his admission to the institution in Gabersee, the pupils did not react to light, the deep reflexes were exaggerated, the speech was difficult to understand, and the gait was unsteady. The patient became slowly more demented and the disturbance of speech more marked. On April 10, 1928, he had a "paretic attack," after which the left arm and leg were paralyzed. The paralysis rapidly disappeared. Two days later, he had another "paretic attack," again followed by left hemiplegia, which remained. During the remainder of 1928 and 1929, he had numerous "paretic attacks" with convulsive movements of the left arm. After this, the dementia gradually became more marked, and the patient was bedridden, except for occasional intervals in which he improved sufficiently to be up and around the hospital. He died on Jan. 31, 1931, with bronchopneumonia.

Necropsy.—This was performed by Dr. K. Neubürger, nine hours after death. The findings were bronchopneumonia, purulent bronchitis, dilatation and hypertrophy of the heart, syphilitic aortitis, verrucous endocarditis of the aortic valve, cystitis and pyelonephritis.

Macroscopic Description of the Brain (Hardened in Formaldehyde).—The meninges were slightly thickened over the convexity. The right half of the brain was about three fourths of the size of the left. The atrophy on the right side was most evident in the parietal and temporal lobes, especially in the supramarginal, postcentral, and first and second temporal convolutions and the insula. The lateral ventricles were dilated, with those on the right about twice as large as those on the left. There was a fine ependymitis of the floor of the ventricles. The blood vessels at the base showed no arteriosclerotic changes.

Microscopic Study of the Brain.—Throughout all portions of the cortex and basal ganglia the changes typical of dementia paralytica were found. The meninges and cortical blood vessels were moderately infiltrated by lymphocytes and plasma cells. In the left hemisphere there was a marked disturbance of the cortical architecture in the frontal lobe and to a less extent in the central convolutions. There was apparent loss of ganglion cells, and many of those remaining showed the severe chronic changes of Nissl. The glia were increased in number, with many rod cells and occasionally protoplasmic astrocytes. Myelin stains of sections from the left hemisphere showed only slight loss of fibers in the cortex of the frontal and parietal lobes, occasionally in the form of localized lesions. The meningeal and cortical blood vessels did not show any arteriosclerotic changes.

In the right hemisphere, status spongiosus or pseudolaminar loss of cells was found in the superior frontal convolutions, the entire temporal lobe, especially at the poles, the island of Reil, and the supramarginal and angular gyri, and to a less extent in the postcentral, precentral and paracentral convolutions. The third cortical layer was the most involved, but in the first and second temporal convolutions, where the changes were most marked, the second, fourth and at times deeper cortical layers were also affected. Status spongiosus was less marked in this case than in the others. The cell loss was more of a pseudolaminar nature or a generalized atrophy. There was an apparent increase of the number of blood vessels in the atrophic cortex, but the degree of perivascular infiltration was less in these areas than in the less atrophic regions. In the fifth and sixth layers of the atrophic convolutions, an occasional ganglion cell was found that showed the reaction previously described (Zellblähungen). There were typical sclerosis of the cornu

ammonis and laminar loss of cells in the third layer of the fusiform gyrus. The occipital lobe showed to a mild degree the typical changes of dementia paralytica. Herxheimer stains showed only a small amount of neutral fat in ganglion cells of the atrophic areas, in the perivascular spaces and in fixed microglia. With the Turnbull blue reaction, a moderate quantity of iron pigment was found in the walls of blood vessels, and in the microglia of the cortex. In the most atrophic areas of the cortex, however, there was practically no iron pigment.

Spielmeyer and Landau myelin sheath stains showed marked loss of myelin in the cortex of the atrophic convolutions. In the white matter there was extensive loss of myelin in the anterior portion of the temporal lobe, with milder loss in the posterior portion of the temporal lobe and in the frontal and inferior parietal lobes. In addition to the diffuse loss of myelin, there were occasional small circumscribed lesions in the white matter of the posterior portion of the first temporal convolution. There was also diffuse loss of myelin in the right internal capsule, as well as striking degeneration of the right pyramidal tract in the medulla.

With the Herxheimer stains there was practically no neutral fat in the lesions in the white matter, with the exception of localized collections of compound granular cells in the posterior portion of the first temporal convolution, where myelin loss was seen with the Spielmeyer stains.

CASE 7.—*A laborer, aged 49, suffered from an illness of approximately three years' duration, characterized by manic behavior, increasing dementia and spells of unconsciousness, with and without convulsive movements; the neurologic and serologic tests were typical of dementia paralytica. Pathologically, there was a diffuse distribution of the changes of dementia paralytica throughout the brain, with, in addition, localized lesions, softening and status spongiosus-like holes in the cortex in the superior and middle frontal convolutions of both hemispheres, the left temporal lobe, the left postcentral and angular convolutions and the anterior portion of the left occipital lobes. Localized and diffuse loss of myelin was present in the cortex and in the white matter of these areas, with fresh "abbau" and marked gliosis in the white matter. There were moderately advanced arteriosclerotic changes in the large blood vessels at the base of the brain and in the sylvian fissure.*

History.—J. H., a laborer, was admitted to the Kuranstalt Neufriedenheim, on June 10, 1927, with the history, given by his sister, that for eight days preceding admission he had been much excited. One night, he came home from Munich and was unable to tell where he had been. On the following day, his speech was difficult to understand and his writing unintelligible. In the past few weeks he had spent a large amount of money, and he wanted to give all his money away. He was very suspicious of the sister, quarreled and complained continuously and was constantly getting into difficulties.

Examination.—On admission, he was excited; an intelligible conversation was not possible. He wanted to leave at once, refused food, had to be forcibly fed and required sedative drugs. The pupils reacted sluggishly to light. The knee jerks and ankle jerks were much increased. The plantar response was normal. There was an articulatory disturbance of speech, but no aphasia was demonstrated. The Wassermann and Sachs-Georgi reactions of the blood were strongly positive. The cerebrospinal fluid showed 136 cells per cubic millimeter; the Pandy and Nonne-Appelt reactions were strongly positive, and the total protein was 0.125 per cent; the Wassermann reaction was negative in a concentration of 0.2 cc., 3 plus in a concentration of 0.6 cc. and 4 plus in a concentration of 1 cc.; the colloidal gold test showed a curve typical for dementia paralytica.

Course.—On June 20, 1927, the patient was inoculated with the organisms of recurrent fever, and responded with a typical fever reaction. Since he failed to improve after the fever therapy, he was transferred to the Heil und Pflegeanstalt, Eglfing, on July 15, 1927. On admission there, he was restless and wanted to get out at any cost. In the course of the next fourteen days, he became much quieter, but was markedly demented and usually euphoric. The monotony of the progressively increasing dementia was interrupted by numerous spells of three varieties: (1) convulsive movements with unconsciousness, after which the speech was more disturbed and the patient was restless; (2) clouded mental states in which he would drop everything, could not speak and was unsteady on his feet, and (3) spells of unconsciousness without convulsive movements, of from two to three minutes' duration, followed by mental cloudiness. In January, 1928, he had an attack, which was not further described, after which the right side of the face drooped. After this, the attacks were accompanied by convulsive movements of the right arm and leg. During the last half of the year 1929, no attacks were recorded. In January, 1930, the attacks occurred daily. The patient died on Jan. 31, 1930, in status epilepticus.

Necropsy.—This was performed by Dr. Neubürger and showed atrophy of the cortex of the brain, diminution of the mass of the white matter, dilatation of the lateral ventricles and numerous peculiar softenings in the gray matter, especially in the frontal lobes and left temporal lobe. The other conditions noted were not significant, except chronic cystitis and pyelitis and dilatation of the heart.

Macroscopic Description of the Brain (Hardened in Formaldehyde).—The brain appeared small. The convolutions were atrophic, especially at the frontal poles of both sides. There was striking atrophy of the middle frontal convolution and of the upper portion of the superior frontal convolution on both sides, the left temporal lobe and the left angular gyrus. The convolutions mentioned, in addition to appearing atrophic, were tinged slightly yellowish; their surface was very irregular, and they felt soft on palpation. In frontal sections of the brain, the cortex of these convolutions was softened. On the left side, this was most marked in the middle frontal convolution, in the second temporal and the angular convolutions, and to a less extent in the first and third temporal, superior frontal and paracentral convolutions. Both lateral ventricles were dilated, the left being considerably larger than the right, especially in the temporal and posterior horns. The right temporal, parietal and occipital lobes did not show any striking changes. There was a fine ependymitis of the floor of the fourth ventricle. The large blood vessels at the base and in the sylvian fissure appeared somewhat thickened and narrow, but no calcified plaques were felt.

Microscopic Study of the Brain.—Sections were taken from all regions of both hemispheres. In addition to the stains used in previous cases, van Gieson's stain, Weigert's elastic tissue stain and the Perdrau stain were used to study the blood vessels. The large vessels at the base of the brain and in the left sylvian fissure were embedded in paraffin and stained with hematoxylin-eosin and van Gieson stains. Throughout the brain the typical changes of dementia paralytica were found. The meninges were everywhere thickened, the pia, and the pial and cortical vessels were infiltrated by plasma cells and lymphocytes. The degree of infiltration was mild and was most marked in the cornu ammonis, the adjacent temporal convolutions and the frontal lobes, and was very slight in the precentral convolutions and the occipital lobes. The Turnbull iron stains showed a large quantity of iron pigment in the microglia and in the blood vessels of the cortex and white matter.

With the Nissl stains there was marked disturbance of the cortical architecture, especially in the frontal lobes, with loss of many ganglion cells in the third layer, and with many rod cells and protoplasmic glia. In the first layer there were numerous fibrous astrocytes. In addition, many of the remaining ganglion cells showed marked degenerative changes. Myelin stains showed diffuse loss of myelin in the cortex and, in addition, numerous small localized lesions in which the myelin sheaths were all lost. With Herxheimer stains there was only a small amount of neutral fat in the ganglion cells and in the perivascular spaces. Many of the larger blood vessels at the base and in the left sylvian fissure showed marked proliferation of the intima, and some of the smaller vessels were nearly occluded. The larger vessels showed degenerative changes also in the media (fig. 11).

In addition to the convolutions showing macroscopic atrophy, the left postcentral convolution and the anterior portion of the left occipital lobe showed the changes to be described, but in a much milder degree than those showing macroscopic atrophy. In the right parietal lobe, a small "Erbleichungsherd" was found

Fig. 11 (case 7).—Proliferation of the intima of the blood vessels at the base of the brain; hematoxylin-eosin stain.

in the sixth layer. In these macroscopically atrophic convolutions there was a slightly atypical softening of the cortex, in which there was a loss of the ganglion cells from the second to the sixth layer with partial replacement by glia cells, chiefly of the gitter type. The softening was most marked at the base of the convolution, extending into the two adjoining convolutions, and was rarely found at the apex. As a rule, the softening was confined to the gray matter, but occasionally it extended a slight distance into the white matter. With the van Gieson stain, these softened areas were shown to be filled with newly formed connective tissue and blood vessels, many of which took the silver impregnation when stained after the method of Perdrau. The gitter cells in the softened area showed a bluish-staining pigment with Nissl stains, and when sections from these areas were stained with Herxheimer's scarlet red, there was a large amount of neutral fat in compound granular cells. With the Turnbull blue stain, many of the cells contained a large amount of iron pigment. Near many of these softenings the cortex showed almost complete loss of all the structures of the second and third layers without glial replacement, giving a picture resembling that of status spongiosus. In this case, also, the peculiar reaction previously described was found in many of the small ganglion cells in the fifth and sixth layers ("Zellblähungen"). A thor-

ough study of the small and large blood vessels in the areas of softening revealed nothing to indicate the source of the softenings. Outside of the fairly marked arteriosclerotic changes found in the large blood vessels at the base of the brain and in the sylvian fissure, no proliferative or degenerative changes were found in the vessels. Serial sections were made of one of the lesions, and no evidence of thrombosis or of emboli was found in any of the vessels. In the vicinity of the

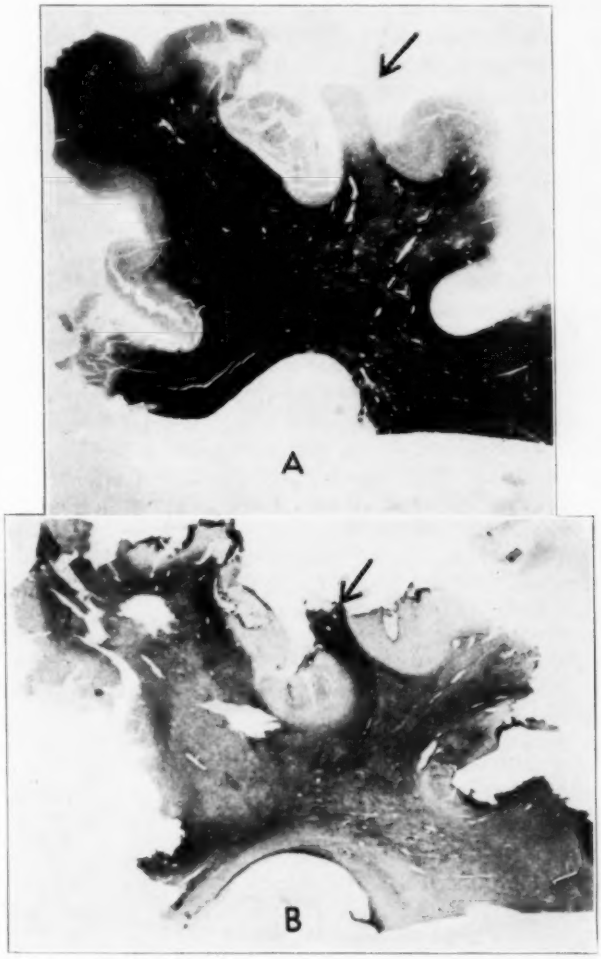


Fig. 12 (case 7).—*A* is a section showing myelin loss in the white matter, Spielmeyer stain; *B*, the corresponding section showing the degree of gliosis, Holzer stain. Note the loss of myelin and the gliosis in the apex of the convolution marked by the arrow.

softenings and the status spongiosus there was proliferation of the fibrous glia, as shown by the Holzer stain, particularly in the first cortical layer. Also there were a few fibrous astrocytes in the softened and in the status spongiosus-like areas.

The white matter of the convolutions mentioned, as well as the underlying area, was rich in glia cells with many "gemästete" glia. In many of the convolutions, particularly in the second and third temporal convolutions, there was diffuse loss of myelin in the white matter. Herxheimer's stain showed signs of fresh "abbau" in the white matter and much neutral fat in the compound granular cells. Similar lesions were found deep in the white matter, circumscribed and not connected with the lesions in the cortex or with adjacent lesions (fig. 12).

The Holzer glia stains showed a much more marked fibrous network than would be expected from the amount of myelin loss, particularly in the sections from the left frontal and temporal lobes.

CASE 8.—*In a man, aged 53 at death, the duration of the illness was two and one-half years; it was characterized by apoplectiform and epileptiform seizures, aphasia, right hemiplegia and partial left hemiplegia shortly before death. Neurologic and serologic examinations gave results typical of dementia paralytica. Pathologically, there were signs typical of dementia paralytica with a rather marked degree of perivascular infiltration, status spongiosus in the cortex and loss of myelin in the white matter of the inferior parietal lobe, temporal lobe, postcentral convolution and anterior occipital convolutions on the left side. The larger blood vessels showed arteriosclerotic changes, and the smaller meningeal vessels showed a moderate degree of Heubner's endarteritis. In addition, there was a mild syphilitic meningitis at the base of the brain and in the spinal cord, and several small granulomas in the cerebellum and medulla.*

History.—G. G., a locomotive engineer, aged 50, was admitted to the Psychiatrische Klinik, Munich, on Dec. 19, 1924, on account of hemiplegia, with mental changes and convulsions. In November, 1923, it was first noticed that there was a change in the patient. He could not make calculations, which was especially noted in handling money. His memory was poor, he was jealous of his wife, and his disposition was bad. He continued to work until Feb. 5, 1924, when he suddenly became unconscious. He was mentally confused for fourteen days afterward; his speech was unintelligible, and he had right hemiplegia. He gradually improved and was able to get around the room by dragging himself with his left hand; he was able also to speak a few words. Six weeks after this stroke, the patient had a generalized convulsion and was unconscious for about five hours. After this he had, at intervals, convulsive movements of the right half of the body. For five weeks before admission, he was bedridden. He cried and laughed without obvious cause.

Examination.—On admission, he was restless, noisy and euphoric. He could not walk or stand up. The right arm was in a position of spastic paralysis. The pupils were irregular and unequal, and did not react to light. The deep reflexes were exaggerated. Speech was not intelligible, owing to a combined aphasic and articulatory disturbance, and his understanding of speech, gestures, etc., was practically nil. The blood pressure was 135 systolic and 90 diastolic. The Wassermann reaction of the blood was 4 plus. The cerebrospinal fluid contained 2 cells per cubic millimeter. The result of the Pandy test was 3 plus and the total protein content was 0.1 per cent; the colloidal gold reaction was 5555432100, and the Wassermann reaction was 3 plus and 4 plus with a concentration of 0.2 cc. and 0.6 cc., respectively.

Course.—The patient was treated with arsphenamine and mercury, without any improvement, and was released to his family on Jan. 9, 1925. He was not readmitted until April 13, 1926. In the interval at home, he had improved at first and was able to get around the house. His speech was limited, however, to a

few curse words, and he was difficult to manage. A few days before readmission, he had another "stroke," and was unable to move the left hand. On admission, examination showed physical signs as before, except that there were paralysis of the right side of the face, weakness of the left external rectus and a Babinski reflex on the right, and that the abdominal and cremasteric reflexes were absent. Speech was still unintelligible, except for a few curse words, which were remarkably clear. There were forced laughter and crying. He improved for a few days, but later became stuporous, showed difficulty in swallowing and in breathing, and died on April 26, 1926.

Macroscopic Description of the Brain.—Dr. Spatz made the following observations: The dura was adherent to the skull. The meninges were thickened over the convexity, and the arachnoid over the basal cistern was thickened. The vessels at the base showed yellowish plaques. The left middle frontal convolution showed a softened area in its anterior portion. The left parieto-occipital region appeared sunken and was soft to touch. The macroscopic iron reaction was 4 plus. After hardening in formaldehyde, the brain was cut in frontal sections, and a marked atrophy of the left parieto-occipital region was clearly seen. The left lateral ventricles were also markedly dilated. The left thalamus was obviously atrophic. There was a marked granular appearance to the walls of both the lateral ventricles.

Microscopic Study of the Brain.—Before considering the changes in the macroscopically atrophic regions, it is necessary to discuss the changes found in other portions of the brain. Throughout the brain the changes typical of dementia paralytica were present. The pia and the pial and cortical blood vessels were infiltrated by a large number of plasma cells and lymphocytes. The cortex of the brain showed everywhere a disturbance of the layers. There was a decrease in the number of ganglion cells, and many of the remaining cells showed severe chronic changes. There was an increase in the number of glia cells. Numerous rod cells and protoplasmic glia were found throughout the cortex. Holzer and other glia stains showed marginal gliosis and many fibrous astrocytes scattered throughout the cortex. In addition to these typical changes of dementia paralytica, there were syphilitic changes in the pia of the brain and spinal cord, in the form of chronic meningitis. This was most intensive at the base of the brain and over the cerebellum. In the cerebellum and medulla several small granulomas were found (fig. 13). Many of the small meningeal blood vessels showed a moderate degree of proliferation of the intima, giving the picture typical of Heubner's endarteritis. The larger vessels showed fairly marked arteriosclerotic changes in the intima and media. There was a striking proliferation of the ependymal lining of the fourth ventricle.

At the pole of the left frontal lobe there were several "Erweichungsherde" of various sizes, which did not, however, involve the entire width of the cortex. In addition to the macroscopically atrophic areas—that is, the left inferior parietal lobe and the adjacent portion of the occipital lobe—the left postcentral convolution and the temporal lobe were microscopically involved in a similar manner. In all of these convolutions there was status spongiosus, which was so advanced in the inferior parietal lobe and adjacent portion of the occipital lobe that no evidences of the former cortical layers were seen. In the temporal lobe, the anterior pole was more severely affected than the posterior. No evidence of active "abbau" was found. With the Holzer stain, there was striking marginal gliosis, and numerous fibrous astrocytes were scattered throughout the atrophic cortex. Many of the ganglion cells that were still present in the atrophic areas showed chronic changes,

and in the deeper layers of the cortex numerous swollen ganglion cells were found ("Zellblähungen"). A small amount of iron pigment was present in the atrophic areas in compound granular cells, but practically none in the walls of blood vessels.

In the white matter of these convolutions and in the deeper white matter, the blood vessels showed a moderate degree of infiltration by plasma cells. With the Nissl stain, the white matter appeared rich in glia cells, which in places were "gemästete" glia. With myelin sheath stains, there was a striking but irregularly distributed loss of myelin in the white matter. The long pathways were not involved. These lesions in the white matter were found without any relationship to the presence or the absence of perivascular infiltration in their vicinity. With the Herxheimer stain, there was a large amount of neutral fat scattered through

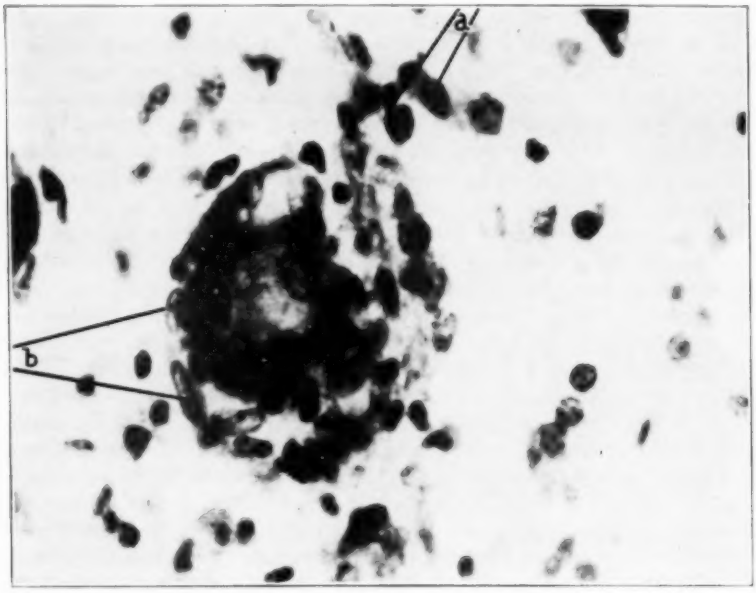


Fig. 13.—A granuloma in the dorsal portion of the medulla adjacent to the twelfth nerve nucleus; (*a*) plasma cells and (*b*) fibroblasts; toluidine blue stain.

the white matter, and Holzer stains showed marked gliosis in the regions showing myelin loss with the Spielmeyer stains.

As was macroscopically evident, the left thalamus showed marked changes. There was a marked degree of perivascular infiltration in the thalamus and the adjacent portion of the internal capsule. Numerous plasma cells were also lying free in the parenchyma. The structure of the thalamus was hardly recognizable, owing to marked loss of ganglion cells and degenerative changes in the remaining cells. A small amount of iron pigment was present in compound granular cells in the thalamus. These changes in the thalamus could not be interpreted other than as primary. Secondary changes were undoubtedly present, but they were obscured by primary changes.

In summary, the distribution and the type of changes in this case were similar to those in the others. Severe changes were found in the blood vessels, partly of the arteriosclerotic type and partly of Heubner's endarteritic type. Whether these

two types of changes have any etiologic relationship will not be discussed here, but the changes in the blood vessels were so marked that their connection with the parenchymal loss must be seriously considered and will be discussed later. The syphilitic meningitis at the base of the brain and in the spinal cord and the granulomas in the cerebellum cannot be related to the dementia paralytica process or to the extreme atrophy of the cortex, and this case must be considered as one showing the relatively rare combination of dementia paralytica and syphilitic changes.

SUMMARY OF THE CLINICAL OBSERVATIONS

A summary of the clinical observations in the eight cases reported is given in table 2. Two of the cases occurred in children,[9] and the average age of all the patients at death was 44 years. The average duration of the disease in the seven cases in which this could be determined was 7.9 years, which is considerably longer than for the

TABLE 2.—*Summary of Clinical Observations in Eight Cases of Lissauer's Dementia Paralytica*

Case	Patient	Age	Sex	Duration of Disease, Years	Attacks		Localizing Symptoms			Therapy
					Epileptiform	Apoplectiform	Hemiplegia	Aphasia	Other	
1	M. M.	48	F	?	+	0	0	0	0	Fever
2	M. I.	63	F	6	+*	+	Right	+	Transient amblyopia	Chemotherapy
3	J. S.	23	M	11	+*	+	Left	+	....	Fever
4	E. M.	16	M	6	+	0	..	..	....	Fever; chemotherapy
5	F. T.	47	M	14	+*	0	0	+	....	Chemotherapy
6	W. K.	54	M	13	+*	+	Left	0	0	?
7	J. H.	49	M	3	+*	+	..	+	Right facial palsy	Fever; chemotherapy
8	G. G.	53	M	2½	+*	+	Right	+	....	Chemotherapy

* Some of the attacks were jacksonian.

usual case of dementia paralytica. All of the cases presented epileptiform attacks, and in six these attacks were at times confined to one half of the body. Hemiplegia was found in four cases, and one of the remaining cases showed paralysis of the right half of the face. In five cases there was an aphasic speech disorder. In several of the cases the first epileptiform or apoplectiform attacks were followed by hemiplegia or aphasia, which disappeared, but with a repetition of the attacks the symptoms became permanent. It can be seen, therefore, that in six cases the clinical observations indicated localization of the process and a clinical diagnosis of Lissauer's dementia paralytica could have been made. In the remaining two cases (1 and 4), this diagnosis could not have been made. In case 1 the patient was under observation only for a short interval, and died of an intercurrent infection before localizing symptoms developed. In case 4 the record was incomplete and contained no adequate description of the convulsions or of the neurologic

9. One of these patients showed the retardation of physical development frequently found in juvenile dementia paralytica.

status. Lissauer's dementia paralytica should be suspected in every case of dementia paralytica with apoplectiform or unilateral convulsive attacks, especially when these are followed by localizing signs, such as hemiplegia, aphasia, hemianopia, etc. In some cases, however, the diagnosis cannot be made during life, particularly if the destructive process is in the relatively silent right temporal and inferior parietal lobes. In differential diagnosis, the only condition likely to be confused with this is meningovascular syphilis with thrombosis. The latter could be differentiated, however, by the absence of convulsions and the difference in the serologic results between this type of case and one of dementia paralytica. The cases of cerebral gumma or of endarteritis of the small cortical vessels might also offer difficulties, but the differences given should help in the diagnosis.

TABLE 3.—*Distribution of the Atrophy in Eight Cases of Lissauer's Dementia Paralytica*

Case	Patient	Side Involved	Frontal Lobe	Temporal Lobe	Central Convolutions		Inferior Parietal Lobe	Occipital Lobe	Insula
					Anterior	Posterior			
1	M. M.	Right	0	+++	0	+	++	0	0
2	M. I.	Left	0	+++	0	+++	++	++	+
3	J. S.	Right	++	+++	++	+++	+++	++	+++
4	E. M.	Right	0	+++	0	0	+++	++	+++
5	F. T.	Both	0	+++	0	0	+++	+++	0
6	W. K.	Right	0	+++	++	++	+++	0	+++
7	J. H.	Left	Right +++ Left +++	+++	0	0	+++	0	0
8	G. G.	Left	0	+++	0	++	+++	++	0

COMMENT ON THE PATHOLOGIC OBSERVATIONS

Macroscopically (table 3), the cases were characterized by outspoken atrophy of certain convolutions, which was remarkably constant in localization. The temporal lobe was usually the center of the atrophy, and the inferior parietal lobe (supramarginal and angular convolutions) was also involved in all cases. In four of the cases, the atrophic process was confined to the right side, in two it was found only on the left side, and in the remaining two it was bilateral. Case 7 was the only case in which the frontal lobes were markedly affected, and in this case the process involved the superior and medial frontal convolutions of the two sides about equally. In case 5 there was status spongiosus in the left temporal lobe, although macroscopically this lobe did not appear markedly atrophic.[10] The anterior central convolution was (in its lower portion) macroscopically atrophic in two cases, while the postcentral was affected in four cases.

Microscopically, the atrophic convolutions showed status spongiosus or pseudolaminar loss of cells, which involved the third and second

10. Fischer (Ztschr. f. d. des. Neurol. u. Psychiat. **7**:1, 1911) made a similar observation in his case 12.

cortical layers and occasionally the deeper layers or the entire cortex. A description of the status spongiosus does not seem necessary; it is sufficient to say that it was characterized by loss of a part of all components of the nerve parenchyma, with an imperfect replacement by fibrous glia (as shown by the Holzer glia stains), resulting in holes of varying sizes in the cortex. Figure 6 shows the appearance of the status spongiosus with the hematoxylin-eosin stain, and figure 7 shows the imperfect replacement of the destroyed tissue by glia fibers. The status spongiosus was usually most obvious at the apex of the convolution, although it was also found at the base. This can probably be explained by the fact that the division of the cortex into its various layers is most evident at the apex of the convolution, and therefore pseudolaminar loss of cells, when present, is most obvious at the apex. In case 3 there was also outspoken status spongiosus of the white matter in the inferior parietal lobe (fig. 5).

In cases 7 and 8 there were moderately marked arteriosclerotic changes in the larger blood vessels at the base of the brain and in the sylvian fissure. There might be some question as to the propriety of including case 7 in this series, as the atrophy was due mostly to an atypical softening process, although status spongiosus was also present. This case was included, however, because the distribution of the process was similar to that in the others and because a thorough study of the case did not reveal any definite relationship of the softened areas to the sclerosis of the vessels, and it was thought that this case would aid in the explanation of the origin of the atrophy in the other cases; it will be discussed further in that connection.

Several details of the microscopic examination warrant further discussion. In all of the cases, a peculiar type of cell reaction was found in the small ganglion cells of the fifth and sixth cortical layers in the convolutions showing status spongiosus in the third and second layers (fig. 1). With the Nissl stain, these cells appeared swollen and rounded; the cytoplasm stained homogeneously pink, and the nucleus was displaced to the extreme periphery of the cell. We realize the possibility of confusing these cells with the so-called "gemästete" glia, but we found numerous transitional forms between the normal ganglion cell and this type of cell, and are convinced of their identity as altered ganglion cells. With Bielschowsky's stain, the body of these cells was homogeneously impregnated and appeared to be filled with fine, dustlike particles. "Argentophile Kugeln" were not found in them. This type of cell reaction has been described in Pick's disease [5] as "Zellblähungen [11]

11. This type of cell reaction has recently been found in a case of dementia paralytica by Müller in this laboratory (Progressive Paralyse mit starker Marksklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **133**:620, 1931).

and has been considered as peculiar to that disease. We think that the cells in our cases are very similar to those in Pick's disease, since the same type of cell (small ganglion cell) was affected. In Pick's disease, these cells occur most frequently in the third cortical layer but, as pointed out by Schneider,[12] with advance of the atrophic process these cells are found only in the deeper layers. In our cases, the degree of tissue destruction was much greater than in the usual case of Pick's disease, and most of the ganglion cells of the third layer had been destroyed. No "argentophile Kugeln" were found in the cells in our cases, but they are not always present in these cells in Pick's disease. This type of reaction is similar to the axonal reaction that has been reported in various diseases,[13] but generally in the large motor cells of the spinal cord and precentral convolution, and it is possible that these types of cell reaction are closely related.

Iron pigment was found in all cases in the walls of the blood vessels and in the microglia of the cortex. This type of distribution of iron pigment is considered by Lubarsch [14] and Spatz [15] as characteristic and pathognomonic of dementia paralytica. Lubarsch [14] stated that the pigment can be found in every case of dementia paralytica, and that it appears in those portions of the brain in which the dementia paralytica process is usually most intensive. Funakawa [16] stated that in general the amount of iron pigment parallels the degree of perivascular infiltration. The origin of the pigment is not known, and Spatz speaks of it as "Paralyseeisen." As stated, iron pigment was found in all of our cases in the typical manner, but little or no iron pigment was found in the areas showing status spongiosus; when found in these regions, it was generally in compound granular cells and not in the fixed glia or in the walls of blood vessels. This would suggest possibly that more iron pigment had been previously present in the fixed glia, but with the rapid destruction of the tissue these cells were also destroyed (or converted into mobile glia), and their pigment content had been taken up by the mobile glia and transported to the blood stream. Against the fact, however, that unusually large quantities of iron pigment were present in these areas, are the facts that the relatively well preserved

12. Schneider, C.: Ueber Picksche Krankheit, Monatschr. f. Psychiat. u. Neurol. **65**:230, 1927.

13. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922.

14. Lubarsch, O.: Ueber die Ablagerung eisenhaltigen Pigments im Gehirn und ihre Bedeutung bei der progressiven Paralyse, Arch. f. Psychiat. **67**:1, 1923.

15. Spatz, H., and Metz, A.: Untersuchungen über Stoffspeicherung und Stofftransport in Nervensystem. II. Mitteilung. Die drei Gliazellarten und der Eisenstoffwechsel, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:428, 1926.

16. Funakawa, Y.: Beteiligung der Sehrinde an dem histopathologischen Prozess der progressiven Paralyse, Arch. f. Ophth. **119**:270, 1927.

areas surrounding the status spongiosus did not contain larger amounts of this pigment than other portions of the brain, and large quantities of iron were not found in the regions where the lesions appeared to be very fresh, as manifested by the presence of a large number of compound granular cells laden with fat. In case 7, the large amount of iron pigment in compound granular cells in the softened cortex most probably had its origin in blood extravasated at the time of the softening, since the quantity of pigment was far too great in comparison with the quantity found in the surrounding areas to be due to the dementia paralytica process alone. It should be mentioned also that in case 3 no iron pigment was found in the atrophic areas, although fairly large quantities were found in sections from the opposite hemisphere. This is emphasized because it occurs to us that had we not made iron stains from the less atrophic areas we should have questioned either our diagnosis or the value of the iron reaction as a diagnostic criterion in this case.

With the exception of case 8, the degree of inflammatory reaction in the meninges and around the cortical blood vessels in these cases was less than that found in the average case of dementia paralytica, and as a rule the degree of perivascular infiltration was less marked in the atrophic areas than in the better preserved regions.

Since the studies of Tuczek,[17] Borda,[6] Fischer[7] and Spielmeyer,[8] it has been known that primary lesions of the myelin in the cortex occur in cases of dementia paralytica. These lesions are of two types: (1) a diffuse loss of myelin in areas showing severe changes in the other elements, and (2) localized lesions very similar to the cortical plaques of multiple sclerosis (Markfleckenbildungen) in areas which may or may not show severe changes in the other components of the cortex. Both of these types of myelin loss were found in the cortex in all our cases.

In regard to the occurrence of myelin loss in the white matter of the cortex in cases of dementia paralytica, little is known. In most of the cases of Lissauer's dementia paralytica reported in the literature, loss of myelin was noted in the white matter of the convolutions, but it was generally considered as secondary to the cortical changes. Spielmeyer[8] and others have reported lesions in the white matter of the spinal cord. Fischer[4] found a striking loss of myelin in the white matter in two of his cases of Lissauer's dementia paralytica, and was of the opinion that it was primary in origin and caused by the same process producing the status spongiosus in the cortex. Bielschowsky[4]

17. Tuczek, F.: Ueber der Anordnung der markhaltigen Nervenfasern in der Grosshirnrinde und über ihr Verhalten bei der Dementia paralytica, Neurol. Centralbl. **1**:315 and 337, 1882.

also found such lesions in a case of Lissauer's dementia paralytica and regarded them as primary. Müller [11] recently reported from this laboratory a case of dementia paralytica showing striking primary loss of myelin in the white matter.

In all our cases there was marked loss of myelin in the white matter. These lesions were localized to certain convolutions, generally those in which status spongiosus was found in the cortex. This was not always true, however, as the myelin lesions were found in regions in which the cortex was not markedly involved (fig. 8). In many instances, evidences of fresh "abbau" could be found in the white matter, whereas in the cortex of these convolutions no evidence of such a process was found. We considered this to indicate that the lesions in the white matter and in the cortex were unrelated in regard to time of origin, and were therefore independent of each other. All of the lesions in the white matter were not of the same intensity, as was shown by the fact that in some lesions the "abbau" was of the mobile type and in others of the fixed type. In both the white matter and the cortex it appeared as if the larger lesions were due to a confluence of numerous smaller ones. This could best be seen with the Herxheimer stain of the rather fresh lesions. Myelin loss was generally found in the white matter of the atrophic convolutions and also deep in the white matter where mixed fibers were present. The long pathways (stratum sagittale externum, fasciculus longitudinalis inferior) were always spared, and we did not find in any case degeneration of the occipitotemporopontile tract, even though the temporal lobe was severely affected. Lesions of the short pathways are common in Pick's disease and in multiple sclerosis, and are considered as primary. On the basis of the facts cited, we agree with Bielschowsky [4] and Müller [11] that this type of lesion in the white matter is primary. This does not, however, mean that all of the myelin loss was primary in origin. Secondary lesions were doubtless also present, as shown by the degeneration of the pyramidal tract in the medulla and spinal cord in several of our cases. We also agree with the opinion of Fischer [4] and Bielschowsky [4] that the lesions in the white matter are morphologically the same and are produced by the same agent as those in the cortex. The failure of status spongiosus to appear more often in the white matter in these cases is due to the difference in the glial content of these regions, as brought out by Spielmeyer.[18] The nature of the glial distribution in the various layers of the cortex also explains why the second and third cortical layers more often show status spongiosus when acutely and severely injured.

18. Spielmeyer, W.: Die Bedeutung des lokalen Factors für die Beschaffenheit der Entmarkungsherde bei multipler Sklerose und Paralyse, Arch. f. Psychiat. **74**: 359, 1925.

COMMENT ON THE GENETIC FACTORS

Since it is probable that the process causing status spongiosus in the cortex was also responsible for the myelin lesions, if we can arrive at the cause of one of these, it will apply also to the other. Spielmeyer [13] stated that status spongiosus is produced by rapid and intensive destruction of all components of the nerve parenchyma and claimed that the factor causing this rapid and intensive destruction need not always be the same. Status spongiosus is found in a number of conditions, namely amaurotic idiocy, senile dementia, Pick's disease, cerebral arteriosclerosis, dementia paralytica and tabes dorsalis, and in the white matter of the spinal cord in subacute combined sclerosis. In amaurotic idiocy and Pick's disease, which are probably endogenous diseases, status spongiosus is diffusely disseminated and of even intensity, whereas in arteriosclerosis and dementia paralytica, exogenous diseases, the process manifests itself in the form of numerous circumscribed lesions.

It is agreed that status spongiosus arises as a result of destruction of all components of the cortex. There is no agreement, however, as to the element initially affected. Fischer [4] believed the ganglion cells to be most severely affected, as persistent myelin sheaths and axis cylinders could be found in the lesions. Sträussler and Koskinas,[19] as well as Bielschowsky,[4] thought the primary change to be in the ground substance, as ganglion cells could be found in the atrophic areas. The cause of this intensive destruction of the cortex has never been definitely determined. Alzheimer [2] and early authors considered it as an extreme intensification of the dementia paralytica process. Fischer [4] did not agree with this theory and postulated the working of some toxin as the cause. He mentioned, however, that several previous authors (Borda,[6] Jakob) had related these changes in individual cases to the blood vessel supply. He excluded this as a cause, however, since the vessels did not show sufficient pathologic change. Bielschowsky [4] directed attention anew to the circulatory factor when he explained the lesions on the basis of serous soaking of the tissue as a result of altered permeability of the cortical vessels. This altered permeability in dementia paralytica, according to Bielschowsky, is due to inflammatory change in the walls of the vessels. Sträussler and Koskinas,[19] in 1926, reviewed the question of status spongiosus and agreed that the most probable cause of the lesion was either that cited in the theory sponsored by Bielschowsky or a functional disturbance of the circulation. In favor of the latter, they cited the occurrence of laminar loss of cells and status spongiosus in vascular diseases.

---

19. Sträussler, E., and Koskinas, G.: Ueber den spongiösen Rindenschwund, den Status spongiosus und die laminären Hirnrindenprozesse, Ztschr. f. d. ges. Neurol. u. Psychiat. **105**:55, 1926.

We have studied our cases in an attempt to decide if these lesions were produced by the dementia paralytica process alone (by direct action of the spirochetes or of a toxin on the parenchyma) or whether one of the factors mentioned also played a rôle.

We first considered the question of the spirochetes. Jahnel [20] stated that he and other authors had found that the most atrophic areas in dementia paralytica are not necessarily rich in spirochetes. Spirochetes [20] have been found in Lissauer's dementia paralytica, but usually not in the most atrophic areas. It is known that localized swarms of spirochetes occur in dementia paralytica, but the lesions produced by them do not differ from those caused by diffusely distributed organisms, with the exception of the rare abscess-like lesions.[21] There has not been any report, however, with regard to the relation of the lesions in the white matter to spirochetes; and although Jahnel [22] had never found spirochetes lying free in the white matter of the brain, it was thought advisable to study these cases in an effort to determine whether spirochetes could be found, and if found what relationship they had to the lesions in the white matter and in the cortex. In cases 5 and 7, numerous small blocks were taken from the most affected areas and stained by the pyridine-uranium method of Jahnel. In the other six cases, large blocks were taken from the affected areas, and frozen sections were cut and stained in Dr. Jahnel's department by the Kufs and Dieterle methods. These preparations were thoroughly studied, but no spirochetes were found in the lesions in the white matter or in the status spongiosus. In one case only, case 4, were any spirochetes found, and these were in the precentral convolution, which was not conspicuously atrophic. The value of this negative observation in these cases is only relative, as the absence of spirochetes in the atrophic areas does not mean that they were not previously present, especially since these patients received modern fever and chemical therapy. Our observations, with those of others,[20] although not eliminating the spirochetes as the cause, would suggest that in all probability the status

20. Jahnel, F.: Pathologische Anatomie der progressiven Paralyse, in Bumke: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

21. Schob, F.: Ueber miliäre Nekrosen und Abscesse in der Hirnrinde eines Paralytikers und ihre Beziehungen zur Spirochaeta pallida, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:588, 1925.

22. Jahnel: Personal communication. Professor Jahnel stated that he had found spirochetes in the white matter of the brain in only three cases. In the first case, he claimed, the observation was questionable, as they were on the border between the cortex and the white matter; in the second case, he found a few spirochetes in the perivascular space of one blood vessel, and in the third case a few were found in the basal ganglia, which were probably in relation to the gray matter of this region.

spongiosus and myelin loss in Lissauer's dementia paralytica are not caused directly by spirochetes.

If the spirochetes are not considered to be the cause of these lesions, it is necessary to decide whether the lesions could be produced by an accentuation of the usual toxic process of dementia paralytica. Against this hypothesis are several facts. First, status spongiosus occurs in numerous conditions unrelated to dementia paralytica and need not, therefore, be caused by the dementia paralytica process. Second, as a rule, the convolutions showing status spongiosus in Lissauer's dementia paralytica are not those in which the dementia paralytica process is usually marked. In the usual cases of dementia paralytica, the process is most intense in the frontal pole and decreases in intensity toward the rear half of the brain, whereas in Lissauer's dementia paralytica status spongiosus occurs mostly in the temporal and the inferior parietal lobe and only occasionally involves the frontal lobe to a marked degree. Third, as already indicated, the quantity of iron pigment parallels the dementia paralytica process, and it seems to us that the small amount (or none) of such pigment in these areas indicates that the lesions are probably not due to the dementia paralytica process alone. Fourth, although it is well known that the degenerative process in dementia paralytica need not parallel the inflammatory reaction in degree, and, further, that the state of the inflammatory reaction found at necropsy does not necessarily represent that at some time previously,[23] we think that the very mild degree of perivascular reaction found in and near the atrophic areas should be given serious consideration in this connection, and probably indicates that the dementia paralytica process was not exceptionally marked in these areas. When all of these factors are taken into consideration, it seems clear to us that some factor in addition to the usual dementia paralytica process must be considered in explaining these lesions.

The other factors to be considered are the serous soaking of the tissue (Bielschowsky) and a functional disturbance of the circulation. In regard to the former, Spatz [24] recently called attention to a statement by Nissl that it is not possible to determine from a microscopic preparation the presence or the absence of edema of the tissues of the brain; we found this statement to be true with regard to our cases. On the other hand, there were numerous points in the clinical history and the pathologic report which, in the light of present knowledge, would indicate that disturbance in the cerebral circulation had occurred in these cases.

---

23. This could also be applicable with regard to the iron pigment, but Lubarsch (footnote 14) has shown that the iron pigment may persist long after the inflammatory reaction has subsided.

24. Spatz, H.: Encephalitis, in Bumke: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

Clinically, all of the cases were characterized by the occurrence of numerous convulsive seizures. Spielmeyer [25] showed that a cerebral vascular spasm is one of the links in the chain of events in the epileptic convulsion, and that this vascular spasm can and often does produce cerebral lesions. It is also important in this connection that in the six cases in which the convulsive attacks were at times unilateral, the status spongiosus was found in the hemisphere opposite to the jacksonian attacks. The most significant clinical observation in this regard would seem to us to be that in many of the cases transient hemiplegia or aphasia was observed after an epileptic attack and that with repetition of the attack these symptoms became permanent. To us there appears only one satisfactory explanation for this observation; i. e., the vascular spasm accompanying the convulsions caused cerebral lesions that became progressively more marked with each succeeding insult. Apoplectiform attacks were also present in five of our cases. Thus, from the clinical data it is apparent that repeated disturbances of the cerebral circulation occurred in these cases.

It is well known that pseudolaminar loss of cells and status spongiosus can be produced by disturbances in the circulation, and considerable evidence [26] was recently brought forth that such lesions occur with functional disturbance as well as with organic lesions of the blood vessels. Scholz [27] recently called attention to the occurrence of such lesions in dementia paralytica and explained the "laminar electivity" of these lesions on the basis of the course of the capillaries supplying the involved layers.

It is noteworthy that in cases 7 [28] and 8, in which there was moderately advanced sclerosis of the cerebral vessels and in which both status spongiosus and areas of softening were found, the distribution of the lesions was the same as in the other cases, in which there were no or only insignificant changes in the blood vessels. This may be

25. Spielmeyer, W.: Die Pathogenese des epileptischen Krampfes, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:501, 1927.

26. Husler and Spatz: Die Keuchhustenekla mpsie, Ztschr. f. Kinderh. **38**:428, 1924. Meyer, A.: Ueber die Wirkung der Kohlenoxydvergiftung auf das Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:201, 1926. de Vries, E.: Acute Diseases of the Brain Due to Functional Disturbances of the Circulation, Arch. Neurol. & Psychiat. **25**:227 (Feb.) 1931. Weimann, W.: Intoxikationen, in Bumke: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

27. Scholz, W.: Zur Frage der Schichtförmigen Veränderungen der Grosshirnrinde, Zentralbl. f. d. ges. Neurol. u. Psychiat. **42**:623, 1926.

28. Benoit recently reported a case of puerperal eclampsia showing softening in the brain exactly similar to that found in our case, and he explained the lesion on the basis of vascular spasm (Ein Beitrag zur Kenntnis der Rindenveränderungen bei Wochenbetteklampsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:602, 1931).

only a coincidence, but recent progress [29] in the investigation of the origin of the lesions in the brains of arteriosclerotic persons without organic occlusion of the vessels indicates that the division between organic and functional disturbances of the cerebral circulation is not so sharp as was formerly considered, and that both can produce the same type of lesion. It must also be remembered that dementia paralytica is a disease accompanied by inflammatory vascular changes, and it has been recently emphasized that functional vascular disturbances are common in such diseases and are probably related to the perivascular infiltration.[30] Spielmeyer [31] recently suggested that such disturbances play an important rôle in the production of certain lesions in dementia paralytica, and one of us [32] showed that sclerosis of the cornu ammonis in dementia paralytica is due to functional disturbance of the circulation. Of the six cases that did not show any significant changes in the walls of the blood vessels, five showed typical sclerosis, and one status spongiosus, of the cornu ammonis.

When we combine the clinical and pathologic evidences, it is clear that functional disturbances of the circulation occurred in these cases. Since it is known that functional disturbance of the circulation produces the same type of cerebral lesions as organic occlusion of the circulation, and since we are unable to explain the lesions in these cases on the basis of the usual dementia paralytica process alone, it seems most likely to us that the lesions in Lissauer's dementia paralytica are due to the effect of disturbance of the circulation on the brain already more or less injured by the dementia paralytica process. This theory was considered, as mentioned, by Fischer [4] and others, but was rejected by them because they could not demonstrate organic lesions in the vessels. In the light of present knowledge this objection no longer appears valid.

This type of lesion should be found more often in cases of dementia paralytica if convulsive phenomena are considered to indicate that a functional disturbance of the cerebral circulation has occurred. Convulsive attacks occur in a large percentage of patients with dementia paralytica, whereas status spongiosus and loss of myelin in the white

29. Neubürger, K.: Arteriosklerose, in Bumke: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7.

30. Spielmeyer, W.: Zur Pathogenese örtlich elektiver Gehirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:756, 1925. Foix, C., and Ley, Jacques: Contribution à l'étude du ramollissement cérébral envisagé au point de vue de sa fréquence, de son siége et de l'état anatomique des artères du territoire nécrose, J. de neurol. et de psychiat. **27**:658, 1927.

31. Spielmeyer, W.: Das Interesse am Studium der Kreislaufstörungen im Gehirn und die Paralyse-anatomie, Wien. klin. Wchnschr. **41**:1011, 1928.

32. Merritt, H. H.: Ueber Ammonshornsklerose bei der progressiven Paralyse und ihren Zusammenhang mit den sogenannten paralytischen Anfällen, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:436, 1931.

matter have been reported in a much smaller percentage. There is no doubt that these lesions, particularly the myelin lesions in the white matter, occur much more frequently than has been previously supposed, and the reason why they have not been found more often is probably because dementia paralytica has been considered only as a cortical disease, and thorough studies of the white matter have not been generally made. With regard to the discrepancy mentioned, it must be emphasized that all functional disturbances of the circulation need not result in irreparable damage to the nerve parenchyma, even though they are accompanied by epileptiform attacks. This would apply particularly to cases such as those of essential epilepsy, in which the brain is not already injured by another process as is the case in dementia paralytica. It may also be possible that the factor of individuality plays an important rôle in the production of such lesions in these cases.

The distribution of the atrophic process in Lissauer's dementia paralytica as shown in our cases and those in the literature (table 1) is remarkably constant, and one is struck by the similarity of this distribution to that in the temporoparietal form of Pick's disease. It should be noted, however, that the first temporal convolution and the cornu ammonis are often spared in Pick's disease, while in Lissauer's dementia paralytica the first temporal convolution is often more severely involved than the other temporal convolutions, and the cornu ammonis is practically always involved. Onari and Spatz [33] pointed out that the areas first affected in Pick's disease are phylogenetically young areas. This would appear to be true also for Lissauer's dementia paralytica, with the exception of the cornu ammonis, but the consideration of Lissauer's dementia paralytica as a systemic disease could not by any means appear feasible, as the distribution of the process is without regard to the boundary of any system. On the other hand, as was first noted by Fischer,[4] the distribution of the atrophy is remarkably similar to the distribution of the branches of the artery of the sylvian fissure. Figure 14, taken from Knoblauch's article on the blood supply of the brain in "Die Allgemeine Chirurgie der Gehirnkrankheiten," [34] shows the distribution of this vessel. As can be seen from the figure, the areas usually involved in Lissauer's dementia paralytica are supplied by the third, fourth and fifth branches. The convolutions supplied by the first and second branches are less often affected. It would appear, then, that in dementia paralytica the cortical vessels arising from the long branches, particularly the posterior ones, of the middle cerebral artery

33. Onari, K., and Spatz, H.: Anatomische Beiträge zur Lehre von der Pickschen umschriebenen Grosshirnrinden-Atrophie (Picksche Krankheit), Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:470, 1926.

34. Bruns: Neue deutsche Chirurgie, Stuttgart, F. Enke, 1914, vol. 11, pt. 1.

are more liable to functional disturbances. Whether this bears any relationship to the known susceptibility of the short perforating branches of the middle cerebral artery to hemorrhage is not clear. It is interesting, however, that Foix and Ley [30] recently showed that organic and functional disturbances in the cortical circulation are much more common in the branches of the middle cerebral artery than in the other two main trunks of the cerebral blood supply. Spielmeyer [31] recently emphasized the fact that there is at present a tendency to overestimate the rôle of the circulatory factor in the production of cerebral lesions, but in view of the observations in our cases we think that the lesions in this type of dementia paralytica are best explained on the basis of a disturbance of the circulation in the branches of the middle cerebral artery.

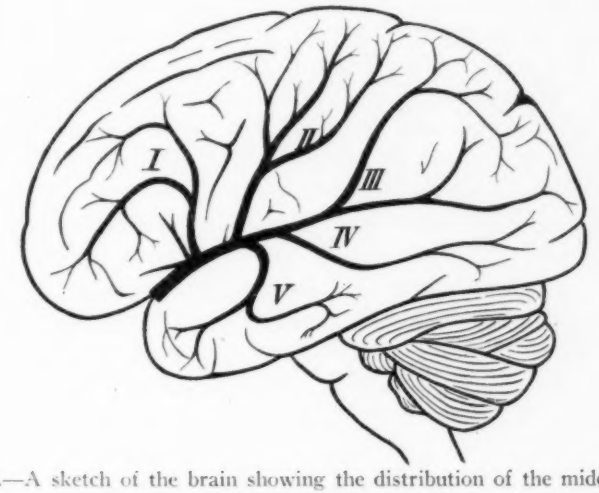


Fig. 14.—A sketch of the brain showing the distribution of the middle cerebral artery. The area supplied by the third, fourth and fifth branches is most severely involved in the Lissauer type of dementia paralytica.

DIAGNOSIS

The characteristic clinical features enabling one to diagnose a given case as being of the so-called "Lissauer's type" have been given, as have also the pathologic observations. Pathologically, there is, as pointed out by Spatz,[35] no sharp dividing line between these cases and the usual cases of dementia paralytica; there are numerous transition forms, and it is only a matter of the extent of the status spongiosus. It seems useful, however, from a clinical standpoint to retain the name Lissauer's dementia paralytica to describe the cases of dementia paralytica with localizing signs.

35. Spatz, H.: Syphilitische Geistesstörungen, in Bumke: Lehrbuch der Geisteskrankheiten, ed. 3, Munich, J. Bergmann, 1929.

SUMMARY AND CONCLUSIONS

1. The clinical and pathologic reports in thirty-five cases of Lissauer's dementia paralytica in the literature are reviewed, and eight additional cases are reported.

2. Our eight cases were characterized clinically by their relatively long duration, the presence of apoplectiform and epileptiform attacks, often jacksonian, and the appearance of localizing signs, such as hemiplegia, aphasia, etc. Pathologically, they all showed macroscopic atrophy, usually unilateral, of certain convolutions, generally in the temporal lobe and inferior parietal lobe. Microscopically, they were characterized by the presence of status spongiosus in the cortex and myelin loss in the white matter of the atrophic convolutions.

3. It is shown that these lesions are not produced by the usual dementia paralytica process alone, and on the basis of clinical and pathologic data it is concluded that they are produced by a combination of functional disturbance of the circulation with the dementia paralytica process. It is pointed out that the usual distribution of the atrophy in these cases agrees with the distribution of the posterior branches of the middle cerebral artery.

4. It is also emphasized that there is nothing to separate sharply this type of case from the "usual" case of dementia paralytica. The differences would appear to be quantitative rather than qualitative. Functional disturbance of the circulation probably occurs in a much larger percentage of the cases of dementia paralytica than is represented by those diagnosed as Lissauer's dementia paralytica. Status spongiosus was found by Fischer [4] in 10 per cent of cases of dementia paralytica, and it is probable that primary loss of myelin in the white matter would be found just as often if more thorough examinations were made.

STUDIES IN SENSATION

II. THE MODE OF STIMULATION OF CUTANEOUS SENSATIONS OF COLD AND WARMTH

H. C. BAZETT, M.D.
AND
B. McGLONE, PH.D.
PHILADELPHIA

Histologic studies have demonstrated that the end-organs of Krause and Ruffini are distributed in the prepuce in numbers similar to those of cold and warm spots, respectively, and that they are found at depths in good agreement with those estimated on physiologic grounds for the end-organs giving these sensations. These end-organs appear to be responsible for these sensations, and the depths of the end-organs sensitive to cold and warmth may therefore be assumed to be those determined for the foregoing end-organs by precise histologic methods, namely, depths of 0.1 mm. for Krause's and 0.3 mm. or more for Ruffini's end-organs, the former close to the most superficial venules, the latter deep to the second venous plexus of Spalteholz.

It has also been demonstrated in a previous paper [1] that measurements of surface temperatures on the two sides of a double fold of prepuce or dorsal skin of the penis allow approximate estimates to be made of the actual temperature change and rate of change at any depth at any given time; so if the depth of the end-organ concerned is assumed, it is possible to compare the initiation of a sensation with the temperature changes that produced it, and to test the validity of the various hypotheses of production of temperature sensations. Weber [2] assumed these sensations to depend on the rate of change of temperature $\left(\frac{d\theta}{dt}\right)$, Hering [3] on the absolute change of temperature and

Submitted for publication, Aug. 6, 1931.
From the Department of Physiology, University of Pennsylvania.

This is the second of a series of three papers on sensation which will be published in this journal.

1. Bazett, H. C.; McGlone, B.; Williams, R. G., and Lufkin, H. M.: Studies in Sensation: I. The Depth, Distribution and Probable Identification in the Prepuce of Sensory End-Organs Concerned in Sensations of Temperature and Touch, With Observations on Thermometric Conductivity in the Prepuce, Arch. Neurol. & Psychiat. **27**:489 (March) 1932.

2. Weber, E. H., in Wagner, R.: Handworterbuch der Physiologie, Braunschweig, F. Vieweg u. Sohn, 1846, vol. 3, p. 549.

3. Hering: Sitzungsb-. d. k. Akad. d. Wissensch., Wein **75**:101, 1877.

Ebbecke [4] on the spatial distribution of thermal gradients. The possibility of an intermediary chemical change has been suggested, by ourselves [5] among others. The data here presented do not imply that some such chemical change may not be the essential factor, but an attempt has been made to determine what are the temperature changes that normally induce stimulation, without any consideration for the present of the intermediary mechanisms concerned.

The data employed are those derived from twenty experiments on the prepuce; the data of many of the experiments were also used in the previous paper.[1] The data are here analyzed on the basis of individual stimulations, with an attempt to correlate variations in reaction time with variations in the recorded temperature changes. In most experiments, from ten to twenty-five stimuli were employed. For analysis, the data of selected but typical experiments have been used. In the experiments designed to test the mode of stimulation, stimuli of varying intensity were used on each side of the fold; in the experiments designed mainly to test the depth of the end-organs, the stimuli were all of moderate intensity. As has been explained in the previous paper, the temperature changes on the more distant surfaces were sometimes similar in magnitude to those on the near surface, more frequently considerably smaller, and variations might be seen even in successive stimuli in the same experiment. Occasionally the temperature changes on the more distant surface might even be greater than those on the near, and, when this was true, such a relationship was frequent for that experimental day. Such anomalies appeared to depend on the presence of large veins, which could be seen in close proximity to the thermocouple on the nearer surface. In favor of such a vascular factor was another anomalous temperature change, which commonly accompanied such conditions, namely, a prolonged change on the near surface after removal of the applicator, and one often greater than that observed during contact. Such anomalies presumably depended on the surface thermocouple being pressed into a groove, so that the temperature attained was modified by the presence of the blood in the vein. Possibly the blood flow was interfered with. On removal of the applicator, true surface temperatures could be recorded, and there might be some exaggeration of temperature changes when the flow of the cooled blood was renewed. The temperature recorded by the thermocouples need not necessarily represent the changes on the surface as a whole, and in such anomalous cases, estimates of temperature changes in the neighborhood of the end-organ must be

4. Ebbecke: Arch. f. d. ges. Physiol. **169**:395, 1917.

5. Bazett, H. C., and McGlone, B.: Am. J. Physiol. **90**:278, 1929.

particularly liable to error. In spite, however, of these difficulties, introduced by vascular factors, the data do present a considerable regularity.

Examples of such anomalous results may be seen in table 1, experiment 1, in which all proximal stimuli (with the exception of 9) gave responses of this type. In stimuli 11, 12 and 16 the point of removal could be accurately read and the temperatures were 0.35, 0.4 and 0.3 C., respectively, higher than those recorded in

TABLE 1.—*Reaction Times to Cold and the Temperature Changes Involved*

					Temperatures						Transmission Time of Temperature Changes		
	Stimulus				Distal Surface			Proximal Surface					Reaction Time of Sensation
Exp. No.	No.	Position	Temperature, C.	Duration, Sec.	Initial	At Maximal Change	Maximal Rate of Change	Initial	At Maximal Change	Maximal Rate of Change	Start	Maximal Rate	
1*	1	D	21.0	3.91	24.30	23.20	0.56	24.40	23.65	0.22	1.35	2.50	1.03
	2	D	21.0	3.94	24.40	23.35	0.49	24.55	23.80	0.17	1.34	1.45	1.67
	3	D	18.4	4.12	23.75	21.75	0.65	23.95	22.35	0.34	1.30	2.45	0.71
	6	D	18.2	3.98	23.50	21.65	0.71	23.60	22.10	0.38	1.15	2.15	0.53
	17	D	17.1	182.10	23.35	17.17	0.52	23.45	17.55	0.61	1.00	1.97	1.49
	4	D	16.8	4.62	23.65	18.60	0.95	23.85	21.25	0.60	0.75	2.30	0.42
	5	D	11.2	3.37	23.05	19.60	1.59	23.15	20.40	0.89	0.80	2.10	0.61
	15	P	21.2	4.49	24.00	23.05	0.22	24.05	23.05	0.25	1.15	1.90	6.05
	10	P	17.0	?	24.20	22.25	0.48	24.25	22.50	0.36	1.00	1.80	2.98
	12	P	17.0	6.24	23.50	20.65	0.51	23.50	20.90	0.38	0.95	1.95	3.42
	11	P	16.7	4.65	23.50	20.55	0.62	23.50	20.85	?	0.70	1.90	2.60
	9	P	11.4	6.95	23.25	17.15	1.22	23.20	16.95	1.58	0.90	1.95	2.43
	16	P	9.2	4.62	23.70	18.45	1.19	23.80	18.65	1.31	0.95	2.15	2.02
2†	1	O	17.0	3.74	29.50	26.85	0.62	29.25	26.10	0.71	0.75	1.72	1.58
	2	O	17.0	4.48	28.80	22.35	2.42	28.55	23.60	0.99	0.62	1.90	1.35
	3	O	17.0	5.30	28.20	26.00	0.33	27.95	25.25	0.54	0.76	1.86	2.46
	4	O	17.0	3.90	27.75	22.65	1.94	27.60	23.50	0.99	0.73	1.67	1.81
	6	I	17.2	4.31	27.60	24.20	0.73	27.40	22.70	1.80	0.75	1.43	0.39
	7	I	17.2	4.18	26.80	23.30	0.75	26.60	19.90	2.99	0.81	1.48	0.41
	5	I	16.6	3.90	27.55	24.80	0.64	27.35	23.30	1.57	0.80	1.60	0.39
3‡	4	D	18.8	5.34	28.05	26.20	0.43	28.40	25.75	0.77	1.56	2.32	0.73
	6	D	18.6	151.50	27.90	20.95	0.60	28.20	22.10	0.77	1.23	1.71	0.65
	5	D	14.8	5.28	29.35	25.40	0.86	29.20	26.50	0.94	1.29	1.71	0.72
	7	P	23.4	6.71	27.90	25.76	0.51	28.20	26.75	0.33	0.86	1.01	7.98
	8	P	18.4	5.28	27.75	25.14	0.53	28.10	25.45	0.69	0.94	1.47	5.73
	10	P	18.0	158.50	27.85	<19.75	0.85	28.10	20.90	0.85	0.68	1.83	5.48
	9	P	14.4	4.65	28.05	23.55	0.85	28.35	25.40	1.38	0.81	1.52	3.32

* Subject 2: fold, 1.15 mm. thickness; cold spot on distal surface and two others at about 5 mm. distance; stimulus 17 represented in figure 6 of previous paper.

† Subject 1: fold 0.95 mm. thick; cold spot on inner surface with two other spots at distances of 4 and 5 mm.; stimulus 3 represented in figure 7. The outer was the distal surface.

‡ Subject 2: fold 1.55 mm. thick with cold spot on distal surface; whole area hyperemic following an experimental stasis of sixty minutes' duration three hours earlier (clamp used which produced some injury from pressure).

the table, which were obtained 3.5, 3.4 and 2.7 seconds later. In experiment 3, in which a large dilated vein was located in the center of the fold, responses of this type were obtained from both surfaces. They were observed also in stimuli 1 and 3 of experiment 2 (fig. 7).

Since errors of this type were sometimes present, no attempt has been made to subject the records to exact mathematical treatment, but the maximum rate of changes has been estimated graphically by drawing tangents to the curves, and the delay at the more distant surface before temperature changes were detectable and before the attainment

of the maximum rate of change was read on the records, and interpolation was then made as described in the previous paper. Errors due to galvanometer lag have been neglected in estimating thermal transmission times, except that in making the readings the earliest possible point has been taken rather than the mean of possible readings. The magnitude of the error from galvanometer lag is shown in figure 4 of the previous paper.[1] It will be seen that in the middle part of the curves the error introduced was such that the true temperature was that recorded by the galvanometer 0.4 second later. In estimating temperature changes at any given time, therefore, rough correction of this error was obtained by reading the curves 0.4 second earlier.

SENSATIONS OF COLD

Cold spots are relatively numerous, and the applicator commonly employed (5 mm. diameter) usually made contact with one or more cold spots on both sides of the fold. Occasionally, cold spots on one side were situated at a sufficient distance so that all stimulations of that surface produced sensations of cold obviously correlated with the temperature changes and end-organs of the further surface. When this was the case, the temperature changes in the region of the end-organ had a gradual onset, and, in correlation with this, the subject found it difficult to distinguish a definite onset of sensation. Consequently, under these conditions, hesitation might be indicated subconsciously in the signal, even though the subject considered that the signal had been made abruptly. (Compare the record of the signal in figure 7 with that shown in figure 6.) In a third group the cold spots on one surface were at some distance, but this was not sufficiently great to prevent an occasional stimulation of the spots on that side as the result of unavoidable variations in the position of application. Only data obtained in the second of these three groups have been subjected to analysis.

Time Taken to Reach the Threshold Stimulus.—The time taken in nervous and motor responses is assumed to be 0.14 second, and the time taken in penetrating to a depth of 0.1 mm. is estimated from the transmission time across the whole fold; when these values are deducted from the reaction time, an estimate of the time taken to reach a threshold stimulus may be made. This time is designated x, as in the equations considered in the previous paper.[1] The values for x so determined may then be compared with the rate of change of temperature observed on the surface nearer to the end-organ, or estimated for a depth of 0.1 mm. from that surface. In the case of cold, where the end-organ is close to the surface, the data give similar curves by either method of comparison. Comparisons with the estimated changes

at 0.1 mm., though more hypothetic, are probably more significant. When the values for x so determined are plotted against the maximum rate of temperature change, a relationship is demonstrable but there is considerable scattering of the data. The time value x becomes infinity when the maximum rate of change is 0.2 C. per second or less; when the maximum rate of change is above 0.7 C. per second, x assumes an almost constant value, though this value varies with the surface stimulated. Since the maximum rate of change appeared the essential factor, further calculations were made of the times taken to reach the threshold stimulus after the maximum rate of change or the fully effective value of 0.7 C. per second had been attained. In direct stimulation, in which the temperature changes start abruptly, the values so determined are almost identical with those determined from the start of the temperature change; in reverse stimulation from the further surface, in which the temperature changes in the region of the end-organ start gradually, values for x determined by the two methods differ considerably, and group better when the time interval for the development of the maximum rate of change is used for the calculation of the value $\frac{d}{v}$.

The values for x so calculated for a single experimental day (table 1, experiment 1) are plotted in figure 1, which shows their relationship to the maximum rates of change of temperature observed on the surface nearer to the end-organ, and also estimated at 0.1 mm. from this surface. The data with direct stimulation group definitely on curves by either method of comparison. Those for reverse stimulation lie on a similar curve at a higher level; a single line represents both curves, since with stimulation from a distant surface the rates of change on the far surface and 0.1 mm. deep to it are indistinguishable. In reverse stimulation, the temperature changes might possibly only be effective if they involved venous blood returning from the further surface, and in this case the transmission time should be calculated on a basis $D + d$, rather than $D - d$, where D represents the total thickness of the fold and d the depth of the end-organ from the further surface. Values so calculated are also plotted in figure 1; the agreement between the two modes of stimulation is slightly improved. If, however, this is the real explanation of the discrepancies in this experiment, it does not appear to be the sole source of such discrepancies, for even when estimates are made for reverse stimulation on a $D + d$ hypothesis, considerable disagreement in the values obtained is often in evidence.

The data obtained in seven experiments (in all of which the more rapid galvanometer systems were employed) are plotted in figure 2, in which comparison is made with the maximum rate of change estimated for 0.1 mm. depth. In six of these seven experiments there were no

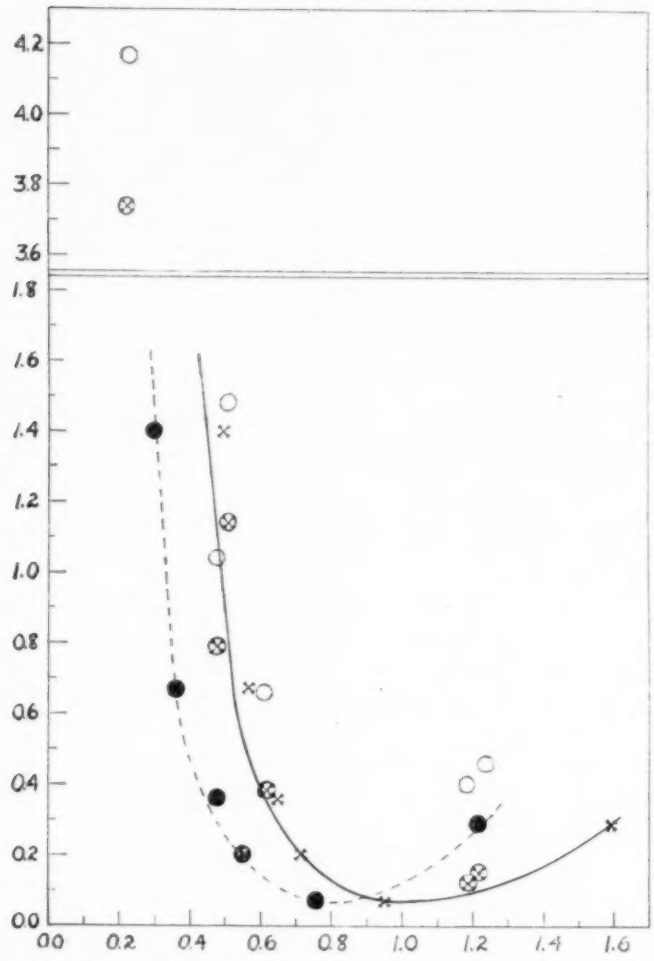


Fig. 1.—Relation of the values of x for cold stimulus to the maximal rate of change of temperature for a single experimental day (experiment 1). The direct stimulation (anatomically distal surface, indicated by crosses and solid line) is compared with the maximal rate of change at that surface: direct stimulation (distal surface, indicated by the solid circles and broken line) is compared with the rate of change at 0.1 mm. depth; indirect stimulation (anatomically proximal surface, indicated by the open circles) on the D—d basis and on the D+d basis (crossed circles) is compared to the maximal rate of change either on the near surface or at 0.1 mm. depth (practically identical). The ordinates represent the values of x in seconds; the abscissas, the maximal rate of change in degrees centigrade per second. The two parallel lines indicate the seconds between 1.8 and 3.6.

cold spots on the area stimulated on one side; in the other experiment cold spots were present on both sides and data on direct stimulation only were obtained. The curve obtained for x on direct stimulation is similar to that of figure 1, and, as in that case, x becomes nearly constant, at rates of change about 0.7 C. per second. The composite data do not give evidence of an increase in the value of x with high rates of change (contrast figure 1). A few values were obtained in the presence of hyperemia, either as the result of a previous experimental stasis or else as the result of repeated puncture during suspension (owing to difficulties in obtaining a fold, one side of which was free from cold spots); these values are specially designated and lie above the curve. A few observations were made during an experimental stasis, and the values so obtained grouped around the curve and are included in the values plotted.

The values obtained with reverse stimulation are more scattered, but appear to fall into three groups through two of which curves have been drawn. Four values from a single experiment (table 1, experiment 2) appear to lie on either side of the curve representing direct stimulation. The intermediate group (2) includes the data of experiment 1 (fig. 1) with the addition of three values from experiment 4 (all obtained with the second position of the thermocouples). Four other values from this experiment fell in the uppermost group. The data of the uppermost curve (3) consist of these four values, and all the data obtained on three other occasions, on two of which hyperemia was noted (table 1, experiment 3). Some factor or factors appear often to cause considerable delay in eliciting sensation with reverse stimulation, even though the rate of temperature change attains a high value, and the delay in the third group cannot be explained by a $D + d$ hypothesis for transmission time. The data of experiment 2 (as well as isolated values from experiments not represented in the graph), when used for calculations of depth d in the previous paper according to the $\frac{d}{v} + y$ equation, gave depths for d of about 0.1 mm.; those belonging to the upper two groups, when similarly treated, gave negative values for d. Some of the variations in the type of response may have depended on the area of the temperature changes on the more distant surface, and the number of end-organs involved.

The Temperature Change Necessary to Excite the End-Organ.— The actual temperature change which has occurred at the initiation of sensation ($\Delta\ \Theta$) has also been estimated. Estimates have been made of the temperature changes on the two surfaces in x seconds. Actual readings were made 0.4 second later, to correct for galvanometer lag, and on the far surface the time measurement was made from the apparent start of the temperature change. The change at 0.1 mm. has

then been estimated by interpolation according to the equation given in the previous paper.[1] The results so obtained in experiment 1 are shown graphically in figure 3, in which the data are plotted as in figure 1, according to the maximal rate of change observed on the surface nearer to the end-organ, and also estimated for the depth of the end-organ.

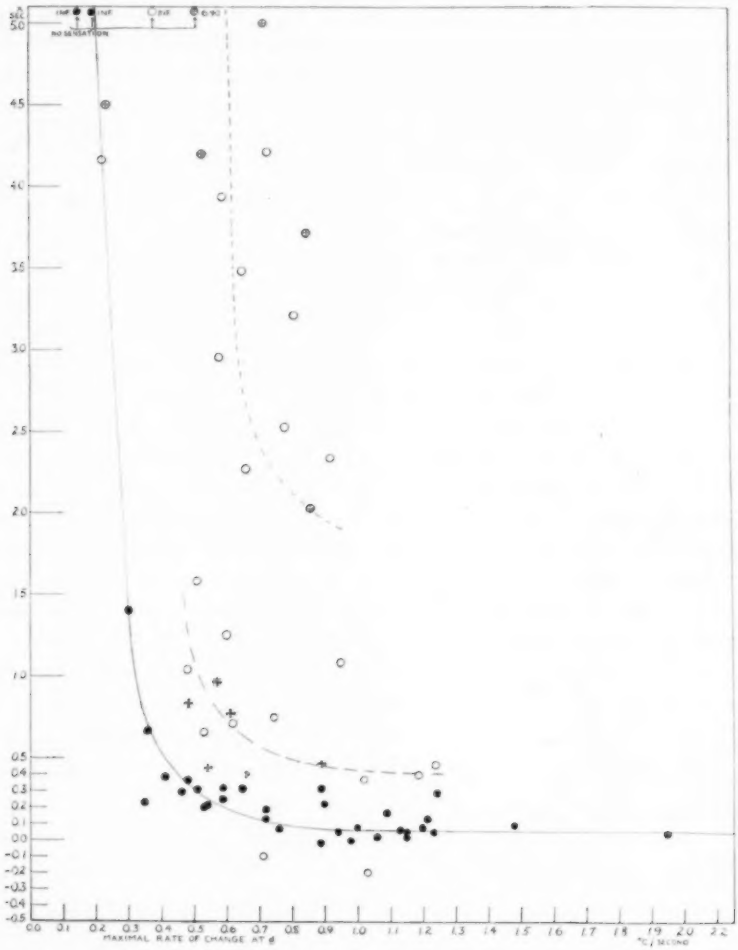


Fig. 2.—Relation of the values of x for cold stimulus to the maximal rate of change at depth d from data of seven experiments. The solid circles and solid line indicate direct stimulation (near surface); the open circles and broken line, indirect stimulation (far surface); the crosses, direct stimulation in the presence of hyperemia; the crossed circles, indirect stimulation in the presence of hyperemia. The ordinates and abscissas are the same as in figure 1. The values plotted with the arrows below them in the upper limit of the figure represent the rate of change recorded without induction of sensation; or in one case, only after 6.9 seconds. Indirect values are calculated on D-d basis.

Both with direct and reverse stimulation, the values tend to group along approximate straight lines, but the temperature change required appears to be about 0.3 C. with direct stimulation and 0.9 C. with reverse stimulation. The contrast in the temperature change necessary to induce sensation according to the surface stimulated was real, and does not depend on inaccurate interpolation. With direct stimulation the surface couple, which must assuredly record a greater temperature change than that of the deeper end-organ, recorded at the induction of sensation a change of 0.64 C. (extremes 0.44 and 1.04 C.), while with reverse stimulation, when this more distant surface couple must assuredly have recorded a smaller change than that at the end-organ, it showed a change of 1.01 C. (extremes 0.66 and 1.61 C.). The temperature change necessary to excite the end-organ must therefore have been at least from 50 to 60 per cent greater with reverse stimulation

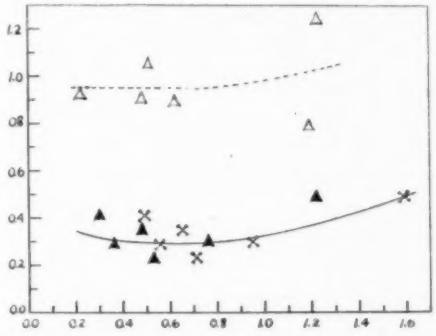


Fig. 3.—Relation of the values of $\Delta\ \Theta$ for cold stimulus to the maximal rate of change in experiment 1. Direct stimulation (anatomically distal surface, indicated by solid triangles) is compared to the maximal rate of change at 0.1 mm. depth, and to the maximal rate of change at the near surface (crosses); indirect stimulation (anatomically proximal surface, indicated by open triangles) is compared to the maximal rate of change at 0.1 mm. depth from the surface nearer to the end-organ. The ordinates represent the value $\Delta\ \Theta$ in degrees centigrade; the abscissas, the maximal rate of change in degrees centigrade per second.

than with direct in this experiment. The data obtained in the seven experiments cited in the previous section are plotted in figure 4. Here also the temperature change necessary to excite on direct stimulation appears to be about 0.3 C., and is increased slightly at the higher rates of change of temperature. In the presence of hyperemia the values are usually somewhat greater. With stimuli near the threshold value, $\Delta\ \Theta$ may also be increased, but it is difficult to attain a threshold stimulus.

With reverse stimulation, the values obtained fall into at least two groups in a manner similar to those observed in the case of the time

value x, but none fall so definitely along the line representing direct stimulation. Many of the values suggest a threshold change under these conditions of stimulation of about 0.9 C., but the values of the upper group (which represent the same data as are represented in the third group of figure 3) show much greater temperature changes which

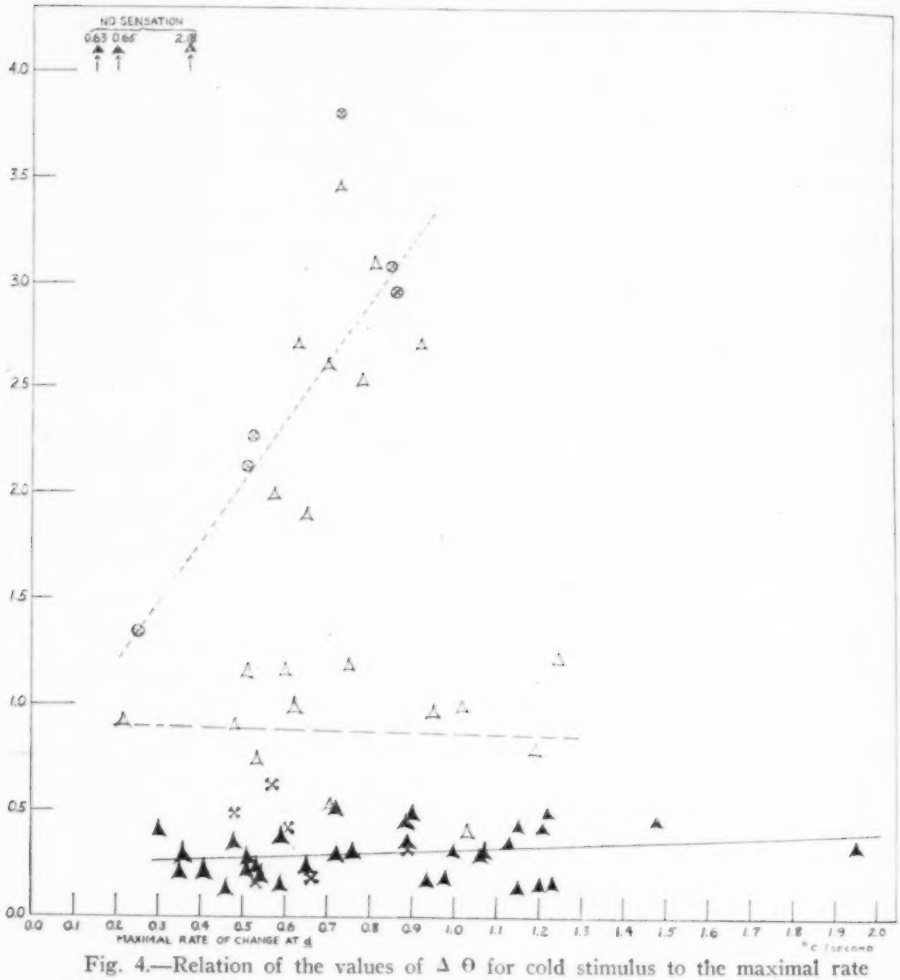


Fig. 4.—Relation of the values of $\Delta\ \Theta$ for cold stimulus to the maximal rate of change at depth d from data of the seven experiments used for figure 2. Direct stimulation (near surface) is indicated by the solid triangle and solid line; indirect stimulation (far surface), by the open triangle and broken line; direct stimulation in the presence of hyperemia, by crosses; indirect stimulation in the presence of hyperemia, by crossed circles. The ordinates and abscissas are the same as in figure 3. The values plotted with arrows at the upper limit of the figure represent the rates of change recorded without induction of sensation; the figures above them represent the total change of temperature produced.

increase rapidly as the stimulus is increased in intensity. Within this group are contained all stimulations when hyperemia was noted. The apparent discrepancy that $\Delta\ \Theta$ increased with increased rate of change while the time value x is much decreased depends on the fact that the latter has been calculated from the time the maximum rate was assumed, when a considerable rise of temperature at a slower rate had already occurred.

Stimuli of Long Duration.—If the temperator was maintained in contact with the surface for several minutes, the sensation of cold elicited at first in subject 1 rapidly developed a maximum, faded gradually, showed fluctuations in intensity, and was barely recognizable toward the end. In subject 2, the results were similar, but the sensation sometimes showed steplike increases in intensity during the first half minute, faded with fluctuations, but always remained appreciable. Figure 5 represents a long stimulus (17) from experiment 1 (subject 2); the maximum intensity of sensation was associated with slow thermal changes, and a later cool sensation with thermal equilibrium. The temperature difference between the two surfaces was much greater than that observed initially and at the moment of maximum sensation twice as great as that observed subsequently. The rates of change on the two surfaces were similar (but that on the near was somewhat distorted by the swinging of the tissue during contact). The cool sensation continued for 0.9 second after removal (near surface rising, far surface stationary) and then faded, and 1 second later a very doubtful after-sensation was recorded. It should be noted that though in this experiment the final temperatures of both surfaces were close to that of the temperator such a relationship was uncommon. More commonly after stimulation had been continued for 2 or 3 minutes the temperature recorded from the near surface differed from that of the temperator by about 1 C., that from the far surface by from 1 to 2 C., and yet the temperatures were no longer changing.

The differences between the two subjects appear real and are evident under other conditions; subject 1 observed no continuing sensation of cold after the hand and forearm had been immersed in circulating water at 9 C. for 14 minutes, while subject 2 experienced cool sensations under these conditions even after immersion for 23 minutes. Under these conditions, subject 1 showed much less hyperemia to cold than subject 2, the color of whose skin was intensely pink.

Influence of Vascular Factors.—Considerable evidence has already been presented that the sensations may be affected by circulatory factors; inflammatory hyperemia has been shown to lengthen the reaction time to cold in the forearm (Bazett, McGlone and Brocklehurst [6]);

6. Bazett, H. C.; McGlone, B., and Brocklehurst, R. J.: J. Physiol. **69**:88, 1930.

similarly the values of x and $\Delta\ \Theta$ are unusually great in the prepuce in the presence of hyperemia. The position of the thermocouples often has a profound effect on the intensity of the sensation, and this may also depend on a circulatory factor. For instance, in experiment 4 a cold spot on the distal surface of a fold from the dorsal skin of the penis gave definite sensations of cold. The thermocouple was placed about 1 mm. from the spot (distal to it as estimated by venous channels) and the second thermocouple was opposite on the other surface

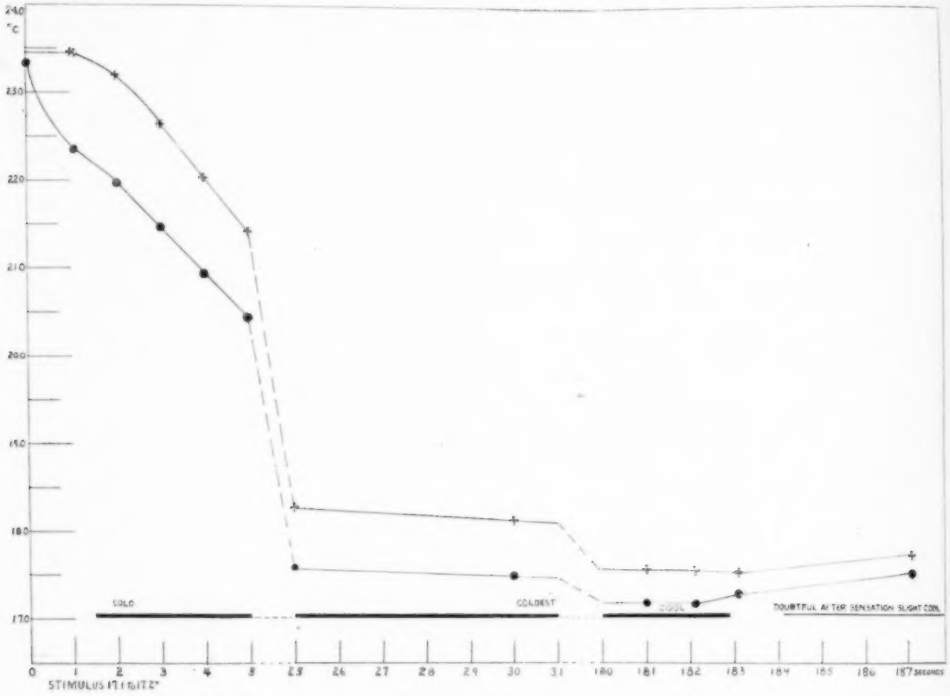


Fig. 5.—Changes in the surface temperatures of near (distal) surface (solid circles), and far surface (crosses) to stimulating temperature of 17.1 C. (stimulus —6.25 C.) in subject 2; the duration of the stimulus was 182.1 seconds. The duration and intensity of the sensations are as indicated. The ordinates represent the surface temperatures in degree centigrade; the abscissas, time in seconds (see table 1, experiment 1, no. 17).

which was free of cold spots. Stimulating temperatures of 17.8 C. and 15.6 C. (stimuli of — 10.7 and — 12.2 C.) which were maintained for 3.6 and 7.6 seconds, respectively, and produced rates of change estimated for 0.1 mm. depth of 1.28 C. and 0.82 C. per second, produced only an unsignaled sensation of "very doubtful cool" and in the second case "very slight cold" after a latency of 6.1 seconds. The

thermocouple on the surface stimulated was then moved to a position 1 mm. proximal (still on the distal surface) to the cold spot. Subsequent stimuli (15.4 to 17.8 C. with rates of change of 0.94 to 1.23 C. per second) gave definite sensations of "sharp cold" with reaction times from 0.24 to 0.36 second. An example may be seen in figure 4 of the previous paper when the reaction time was 0.30 second.

Stasis was produced on one occasion by the use of a light clamp (of intestinal type) and was maintained for an hour. The surface temperatures fell but little, possibly owing to their previous low levels and the presence of warm air currents from the body, though some slight circulation may have been present. The clamping caused pain and, when this had subsided, definite brisk sensations of cold with normal values for x were obtained with direct stimulation. After-sensations were of slight intensity. With reverse stimulations 9 minutes later, the sensation was of gradual onset, very slight and the reaction time was 7.5 seconds in spite of a rapid rate of change. A later reversed stimulation only produced a transitory sensation of cold, 10.3 seconds after application. Stasis appeared to interfere with reverse stimulation.

On release of stasis, pain interfered with any estimation of other sensations for some time; marked hyperemia was in evidence, but the temperatures rose but slowly; initial temperatures of 26.63 and 26.99 C. became 26.66 and 26.82 C. in 1 minute, 27.16 and 27.21 C. in 2.3 minutes and 28.56 and 28.68 C. in 18 minutes. Marked hyperemia was in evidence after a few seconds. The reaction times for sensation with reverse stimulation remained long (7.1 and 6.2 seconds). The data of experiment 3, table 1, were obtained on a cold spot in the same area 3 hours later, when hyperemia had not subsided completely.

After-Sensations of Cold.—After-sensations of cold or cool, often definite, were usually observed (fig. 6) and were similar to those of the forearm (Bazett, McGlone and Brocklehurst[6]). After-sensations were often correlated with slight secondary temperature changes; where the secondary change occurred early after the removal of the temperator, as in the cases considered previously, primary and secondary sensations were fused, even though the secondary fall of temperature might be recorded on the surface distant from the end-organ (fig. 7). If the secondary change occurred later (fig. 6), the after-sensation was usually separate. The secondary waves might be so slight that the temperatures on both surfaces continued to rise, though more slowly than previously, and after-sensations have often been recorded with steadily rising temperatures without evidence of secondary waves. They might be accounted for by lateral spread to neighboring end-organs, and after-sensations are sometimes definitely referred by the

subject to another area. However, in subject 1 a definite after-sensation has been experienced at the end of a stimulus of 150 seconds' duration, where peripheral spread must have been already practically complete, though in subject 2 long stimuli have usually given very indefinite after-sensations.

Paradoxical Sensations of Cold.—Sensations of this type produced by hot stimuli have been common during preliminary tests; after the thermocouples have been placed in position they have been no longer observed, even though inflammation of the type described in the forearm was absent.

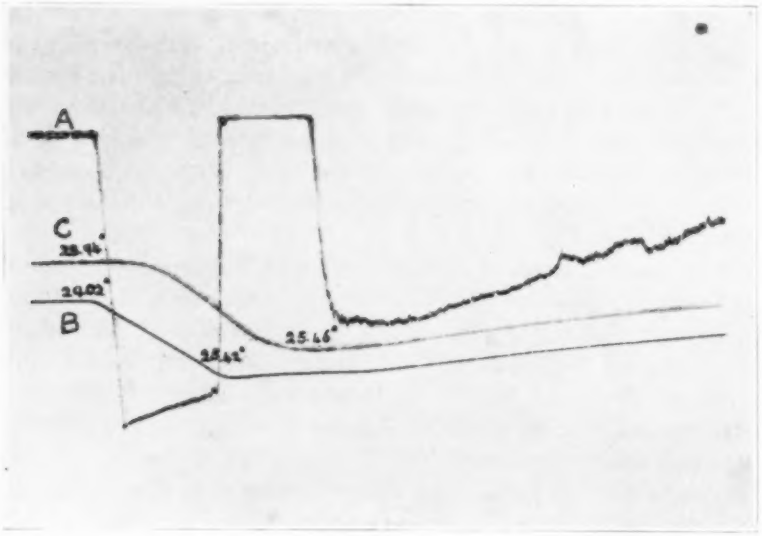


Fig. 6.—Record of experiment on subject 2. A stimulating temperature of 16.4 C. (stimulus, —12.62 C.) was applied to the distal surface of a fold 1 mm. thick for 5.5 seconds. *A* indicates the subjective record of sensation (downstrokes), primary, "very cold," secondary "cold" becoming "cool" which is continued throughout the portion of the record reproduced; the interruptions indicate seconds. *B* is the record of temperature changes on the near (anatomically distal) surface of a dorsal fold. *C* is the record of temperature changes of the far (proximal) surface. There are three cold spots on the distal surface within the area of the applicator surface, and probably one cold spot opposite on the proximal surface.

Comparison with Data Obtained on the Forearm.—The data obtained in the prepuce, together with those reported by Endres (1930) for the forearm, allow the conclusion to be drawn that the end-organs for cold exist also in the forearm at about 0.1 mm. depth. Consequently, the data already presented (Bazett, McGlone and Brocklehurst [6]) may now be analyzed in regard to the nature of the stimulus. In figure 6

of that paper the temperatures at four levels were recorded and these curves have been measured on a comparator at 0.2 second intervals, and have been plotted (fig. 8) to show actual temperatures in relation to time. Corrections have been made not only for parallax, but also approximately for galvanometer lag on the basis of the distortion indicated in figure 1 of that paper. In figure 9, the same data are used to indicate the probable spatial gradients in the tissues at various times. The curves representing spatial gradients have been drawn through the four points at which temperatures were measured, and have been completed on the assumption that the cold wave continues to progress slowly inward after removal of the applicator, and that in this progress the thermal gradients become less acute, and the whole general level returns toward the normal. Analyses of numerous records have demon-

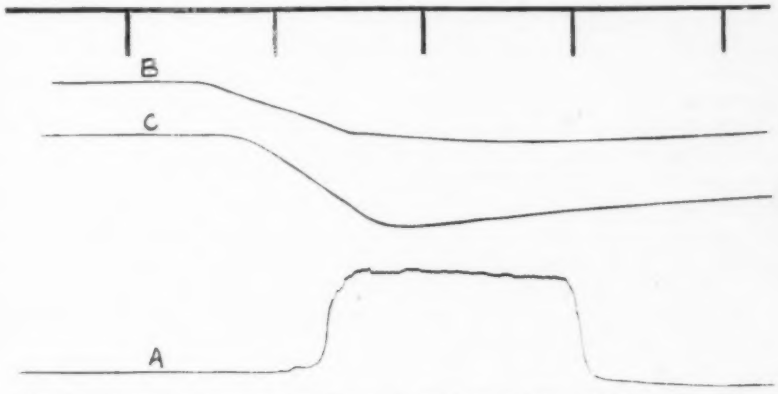


Fig. 7.—Record of experiment 2, no. 3, subject 1 (see table 1). For description, see the text. *A* is the subjective record of sensation, duration of upstroke, "slight cool, apparently very late onset, continuing after removal of applicator." *B* is the record of temperature changes of the near (outside or distal) surface. *C* is the record of temperature changes of the far (inside or proximal) surface. The temperature factor in record *B* was approximately 2.018 C. in record *C*, 1.865 C. per centimeter. The cold end-organ was nearer the far (inside or proximal) surface (record *C*). The vertical lines at the top of the record indicate 5 second intervals.

strated the possibility of reverse gradients at depths greater than that of the subpapillary arteriolar plexus during this recovery period. It is assumed that the warming of the surface occurs through blood entering from this plexus at a depth of from 0.8 to 1 mm. No evidence has been obtained of reverse gradients in the region superficial to this, although the venous plexuses might contain blood at a low temperature. In the later period of recovery, the temperatures at the surface and at 0.95 mm. depth are almost identical, and the rise in tempera-

tures occurs at the same rate at these two levels; a plateau type of gradient must exist, so that the dermis shows the type of gradient seen in dermis and subcutaneous tissue at a later stage after cold bathing (Bazett and McGlone[7]).

During stimulation, a relation of the temperature changes to one another at different depths, similar to that observed in the prepuce, may be seen if allowance is made for the compression of the tissues by the thick surface couple during stimulation, and by this means an approximate estimate of the temperature change at 0.1 mm. at the time sensation is induced may be made.

In making such estimates, the following assumptions have been made: The heavy surface couple is considered to be depressed 0.25 mm. into the skin and to represent temperatures at this depth during application, and actual surface temperatures in recovery. The tissue between the surface and the end-organ for cold is considered as relatively incompressible. The maximum temperature change is reached when the gradual subsidence of the whole wave balances the effect of its inward movement (i. e., when the peak of the curve plotted on a spatial gradient basis is slightly superficial to the depth under consideration). The time at which the maximum change is reached at any given depth may be approximately estimated by interpolation, for by observation the times at which this maximum is reached after the removal of the stimulus were: surface, 0.00 second; 0.95 mm., 5.0 seconds; 2.1 mm., 16.2 seconds, and 4.8 mm., about 55 seconds; these give an approximate straight line when both time and depth are plotted logarithmically. Times for a warm stimulus (fig. 14) showed a similar relationship; they were: surface, 0.00; 0.95 mm., 3.1; 2.1 mm., 15.85, and 4.8 mm., about 50 seconds. In comparing the start and end of sensation with thermal changes, a correction of 0.14 second has been made for nervous processes.

The value for $\Delta\ \Theta$ appears to be 0.50 C. (with a maximum rate of change of 2.3 C. per second) which corresponds well with the prepuce data in the presence of slight inflammation. Sensation after removal of the applicator appears to be prolonged in spite of an actual rise of temperature in the whole area to 0.3 mm. depth unless the presence of a wave of cooled venous blood be assumed. The after-sensation appears to be elicited at a time when the temperature of the superficial layers is rising more slowly than has been the case a little earlier, and with no evidence of any sudden modification of the gradients in this area.

Lateral spread is hard to measure in the prepuce since radiation affects the surface couples, but in the forearm the effect of lateral spread on buried couples may be measured. In one such experiment, with thermocouples at 0.65 and 2.6 mm. depth, with an applicator of 1.5 mm. diameter and a stimulating temperature of 19.7 C. (stimulus, —14.6 C.), on direct stimulation (8 seconds) the more superficial

7. Bazett, H. C., and McGlone, B.: Temperature Gradients in Tissues in Man, Am. J. Physiol. **82**:415, 1927, figs. 12 and 13.

couple showed a fall of 3.3 C. and the deeper 0.75 C., and a sensation of "cold" was induced 0.2 second before the start of the change in the superficial couple. An after-sensation of "cool" was noted 2.3 seconds after removal. With the stimulus applied 3.5 mm. laterally (10 seconds' duration), the changes were —0.85 C. and —0.42 C., without eliciting sensation. With the stimulus applied 5 mm. laterally (12

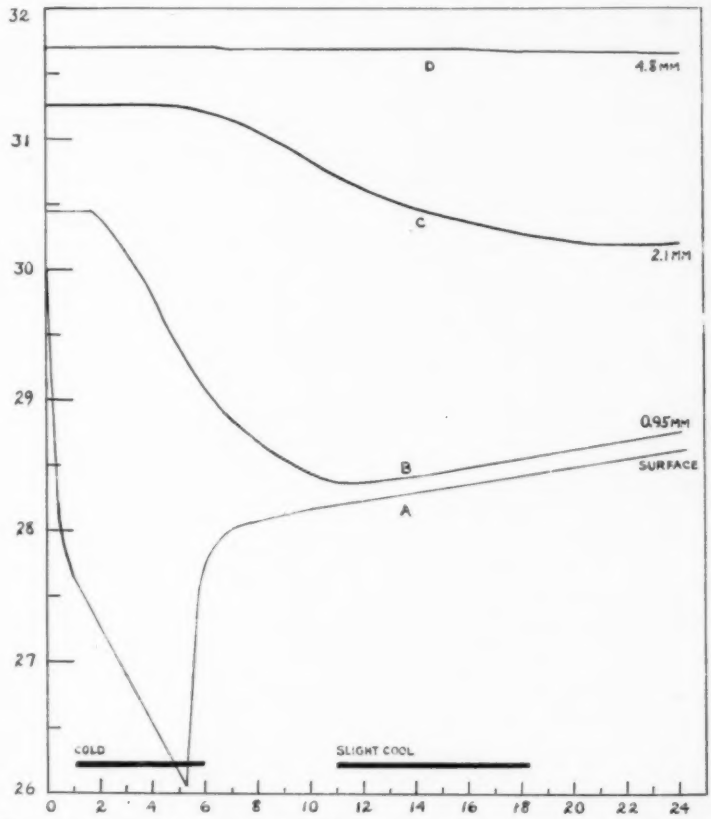


Fig. 8.—Corrected curves from the record of the changes of temperature on surface (*A*), and at depths of 0.95 (*B*), 2.1 (*C*) and 4.8 mm. (*D*) in the forearm. The stimulating temperature was 18.4 C. (stimulus, —11.6 C.); the duration, 5.4 seconds. The sensations are as noted. See the text for description. The ordinates represent the temperature in degrees centigrade; the abscissas, time in seconds.

seconds' duration), the changes were —0.22 C. and —0.16 C. without sensation. The rates of change at the two depths in direct stimulation were 0.99 and 0.13 C.; with the stimulus applied 3.5 mm. laterally, they were 0.10 and 0.02 C. per second.

When a cold stimulus was applied in the forearm during stasis, primary cold sensations were always induced but were never followed by after-sensations except in a single experiment where needle thermocouples of considerable thermoconductivity were used, and the after-sensations experienced were referred to the needle paths. On release of stasis, after-sensations might be again definite, but in the presence of hyperemia of this or other origin they were often absent.

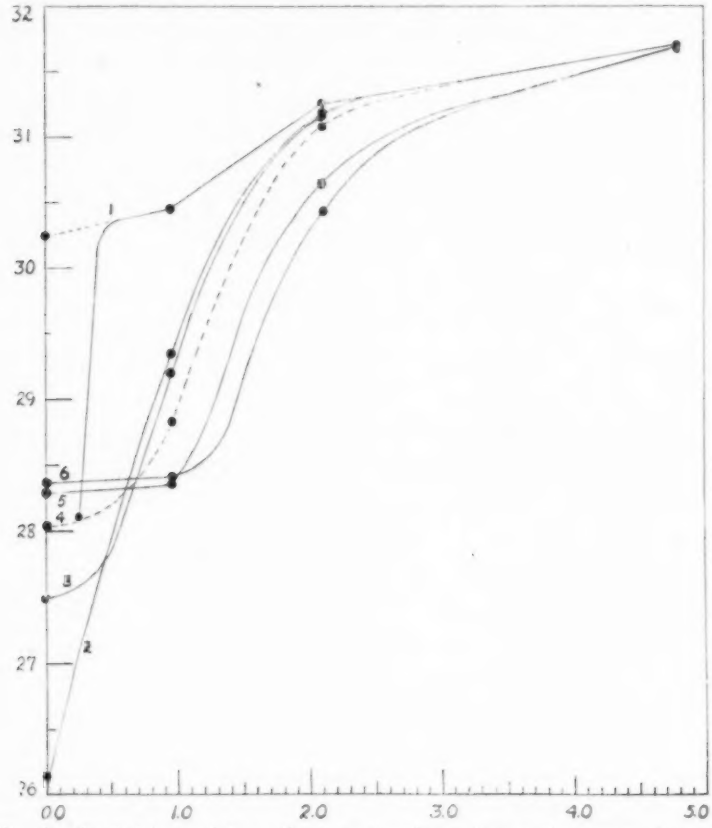


Fig. 9.—Probable spatial gradients in the tissue during the temperature changes shown in figure 8 at (*1*) fore-period and start of sensation, (*2*) end of stimulus, and (*3*) 0.5 second, (*4*) 2 seconds, (*5*) 8 seconds and (*6*) 16 seconds, respectively, after the end of the stimulus. The solid lines represent the gradients during sensation; the broken lines, a gradient between the end of the primary and the appearance of the secondary sensation. The ordinates represent the temperature in degrees centigrade; the abscissas, depths in millimeters.

SENSATIONS OF WARMTH

Since warm spots were relatively few in number, complication of the results by the possibility of stimulation of end-organs belonging to

both layers of the dermis was rare. On the other hand, the greater depth of the end-organ made it impossible to estimate the rate and amount of change in temperature from that of the nearest surface, and all deductions depend on interpolation.

Time Taken to Reach the Threshold Stimulus.—The time value (x) has been calculated as for cold, but it has been estimated on the basis of the transmission time to the commencement of the temperature change, since the end-organ for warmth appeared to be sensitive to even small rates of change. If the time to maximum rate of change was employed, many negative values for x were calculated. Occasional negative values were obtained using the other criterion, but they were

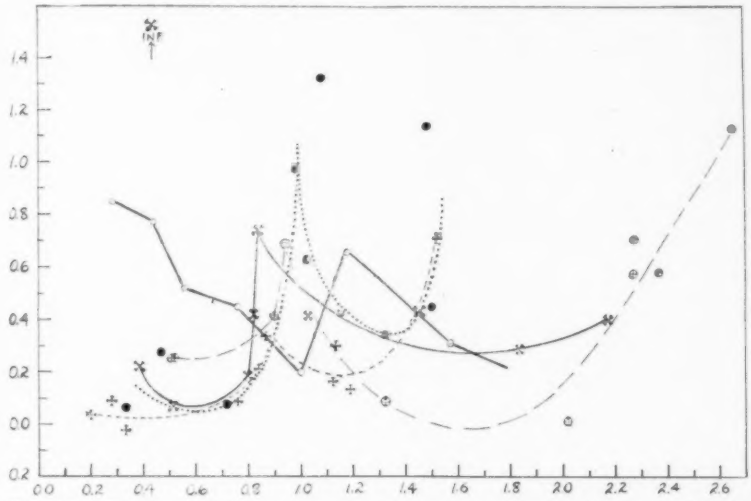


Fig. 10.—Relation of the values of x for warm stimulus to the maximal rate of change at depth d. The data are plotted as follows: experiment 5, subject 1, direct stimulation, crosses and solid lines; experiment 6, subject 2, direct stimulation, solid circles and dotted line; experiment 7, subject 1, direct stimulation, crosses and broken line; stimulation of the other surface (probably also direct), crossed circles and dotted lines. The heavy solid line is drawn through the coordinates (circle and dot) of the mean values (direct stimulation) for six experiments. In experiment 5, the room temperature was about 27 C.; in experiments 6 and 7, 21 C. The ordinates represent the value of x in seconds; the abscissas, the maximal rate of change at depth d in degrees centigrade per second. The value plotted with an arrow below it near the upper margin represents the rate of change in a stimulus giving no sensation.

of small magnitude even though the data showed a wide range of variation. Data obtained in two experiments (5 and 6) are given in table 2. In figures 10 and 11, mean values for all data obtained in warm rooms (six experiments) are plotted for comparison with the individual data of experiment 5 (warm room) and experiments 6 and 7 (cold room).

EXPERIMENT 7.—*Subject 1.*—The fold of skin was 1.3 mm. thick. The reaction time of sensations averaged, distal (outside), 0.51 C., and proximal (inside), 0.63 C., but the sensations were much more intense with a stimulus on the inner surface. The transmission time was 57 per cent longer from outside to inside than in the other direction, and the depth calculated was 0.43 mm. from the outside. But such calculation on the basis of one end-organ gave many negative values for x and consequently in view of the nature of the sensation, the presence of end-organs on both surfaces, each at a depth of 0.3 mm., was assumed. In favor of the validity of this assumption is the close agreement with values calculated from experiment 6 (table 2), when the room conditions were similar.

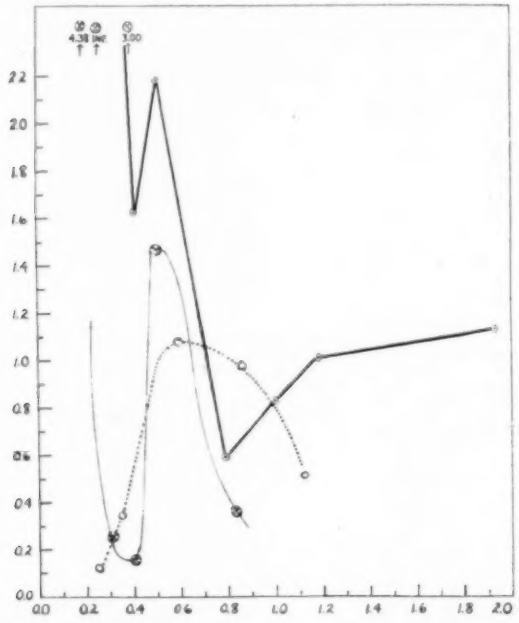


Fig. 11.—Relation of the values of x for warm stimulus to the maximal rate of change at depth d. The values are plotted as follows: experiment 5, subject 1, indirect stimulation, crossed circles and solid line; experiment 6, subject 2, indirect stimulation, open circles and dotted lines. A heavy solid line is drawn through the coordinates (circle and dot) of the mean values for six experiments (indirect stimulation). For room temperatures, see the subscription to figure 10. The ordinates and abscissas are the same as in figure 10. The values plotted with arrows below them near the upper margin represent the rates of change that gave no sensation (central value) or sensation only after 4.3 seconds (left) and 3 seconds (right).

With slow rates of change in temperature, the time value x was increased, particularly in reverse stimulation. The sensitivity to slow rates of change often appeared at least twice that of cold, but the limiting rate, below which sensation was absent, was variable. Evidence of variations, probably associated with vasomotor adjustments, was

TABLE 2.—*Reaction Times to Warmth and the Temperature Changes Involved*

Exp. No.	Stimulus: No.	Position	Temperature, C.	Duration, Sec.	Temperatures: Distal Surface: Initial	At Maximal Change	Maximal Rate of Change	Proximal Surface: Initial	At Maximal Change	Maximal Rate of Change	Transmission Time of Temperature Changes: Start	Maximal Rate	Reaction Time of Sensation
5*	1	O	30.5	9.3	27.70	30.20	0.47	27.90	29.20	0.25	1.13	1.13	....
	3	O	35.1	4.6	27.45	31.15	2.10	27.40	28.60	0.27	1.47	1.47	1.45
	6	O	35.1	5.0	27.80	31.45	1.23	27.70	30.10	0.36	1.17	1.32	3.96
	2	O	35.1	6.4	27.15	31.50	2.07	27.20	28.35	0.16	1.22	1.54	5.38
	7	O	37.3	179.0	27.90	36.75	1.67	27.75	34.20	0.36	0.99	1.55	1.05
	5	O	41.1	5.5	27.95	34.10	1.68	27.95	31.05	0.78	1.30	1.43	1.23
	4	O	41.1	5.7	27.55	34.55	3.34	27.70	29.35	0.42	1.86	2.09	2.91
	13	I	31.5	4.6	28.40	29.20	0.44	28.50	30.10	1.88	1.32	1.32	....
	12	I	31.5	7.0	28.25	29.45	0.25	28.50	29.95	1.45	0.99	1.10	0.66
	11	I	35.3	4.9	28.20	29.75	0.37	28.40	30.35	1.37	0.97	1.43	0.50
	10	I	35.4	5.0	28.00	30.10	0.48	28.05	31.20	3.44	1.04	1.87	0.64
	9	I	37.3	4.3	28.30	29.75	0.64	28.50	30.95	1.66	0.60	1.48	0.76
	8	I	37.4	3.8	28.65	31.05	0.66	28.85	32.45	3.63	0.75	1.32	0.77
	17	I	39.0	112.0	28.80	37.60	1.26	29.00	38.20	7.77	0.77	1.10	0.66
	16	I	39.0	163.0	28.90	35.35	0.60	29.00	37.25	2.71	1.17	1.76	1.23
	15	I	40.8	3.8	28.85	33.40	1.45	28.95	35.25	6.88	0.60	1.10	0.72
	14	I	40.8	4.4	28.60	31.75	0.89	28.70	35.05	7.34	0.85	1.32	0.83
6†	8	D	28.0	12.8	24.05	27.05	0.54	24.15	26.70	0.23	1.65	2.47	0.43
	7	D	29.2	11.6	24.15	27.80	0.71	24.35	27.45	0.35	1.59	2.29	0.63
	6	D	32.4	8.5	24.00	29.15	1.37	24.05	28.10	0.44	1.61	2.44	0.44
	3	D	34.8	8.0	24.10	30.50	1.60	24.35	29.00	0.68	1.47	2.57	1.31
	5	D	35.4	6.1	24.05	29.65	1.48	24.15	28.25	0.76	1.54	2.83	0.98
	4	D	35.6	5.8	24.20	29.95	1.74	24.35	28.55	0.74	1.49	3.14	1.66
	16	D	37.5	30.0	24.35	36.95	3.39	23.70	32.85	0.79	1.72	2.31	1.52
	17	D	38.0	123.0	24.00	>37.75	1.96	23.75	>33.45	0.77	1.38	2.24	0.76
	1	D	40.4	6.0	24.80	>31.60	2.21	25.05	>29.90	0.90	1.41	2.71	0.67
	2	D	40.6	4.1	24.40	30.90	2.60	24.75	28.55	0.99	1.35	2.54	0.77
	10	P	27.5	12.6	23.65	26.10	0.24	23.95	27.90	1.43	1.34	1.73	1.42
	9	P	28.0	12.9	23.85	26.75	0.33	24.10	28.90	2.65	1.24	2.62	1.56
	11	P	32.6	10.3	23.60	28.55	0.48	23.90	30.30	3.36	1.32	2.64	11.20
	12	P	33.4	11.3	23.80	29.70	0.56	23.95	30.45	3.44	1.26	1.92	2.31
	13	P	36.0	9.6	23.75	30.10	0.80	24.25	30.90	7.61	1.12	2.55	1.99
	15	P	37.4	125.0	23.45	35.95	0.83	23.45	33.55	5.87	1.70	3.15	5.27
	14	P	42.0	4.1	23.80	28.50	1.05	24.40	31.00	6.89	1.04	2.25	1.56
	18	D	37.5	120.0	23.55	37.40	3.14	23.25	33.25	0.88	1.70	2.69	0.86
	19	D	39.2	123.0	23.10	39.40	5.55	23.10	36.85	1.02	1.33	2.22	1.98
	20	P	39.0	124.0	23.45	37.05	0.83	23.40	37.30	6.11	1.87	3.18	2.53
	21	P	40.8	8.7	25.85	32.00	0.79	25.70	36.25	5.20	1.87	3.08	3.57
	22	P	33.2	11.7	26.60	29.35	1.00	26.20	31.30	2.58	1.65	2.97	1.26
	23	D	33.2	16.6	26.80	32.20	2.78	26.15	29.20	0.33	2.36	2.97	2.47
	24	D	40.8	16.2	27.00	36.50	2.35	26.10	31.55	0.60	2.20	3.08	1.21

* Subject I: fold, 1 mm. thick; warm spot on inner surface. Stimuli 1 and 13 gave no definite sensations of warmth; 2 gave only an uncertain sensation; in 4, the temperator was badly centered; 7 gave fluctuating sensations persisting until 1.5 seconds after removal; 17 gave an initial warmth followed by fluctuating sensations of slight intensity and indefinite fading several seconds after removal; 16 was complicated by light contact and movements of the prepuce across the temperator with respiration; in 7, 16 and 17, after-sensations were signaled but were doubtful in 17; room temperature (dry bulb) was approximately 27 C.

† Subject 2: fold, 1.9 mm. thick; warm spot on distal surface. Stimulus 11 noted as bad contact and values not utilized; 15 disregarded in plotting figure 12; long stimuli 17 and 15 gave persistent sensations of diminishing warmth ending about 4 and 3.35 seconds, respectively, after removal; in 16 the contact was irregular. Records 18 to 20, inclusive, were obtained with stasis (5, 19 and 30 minutes after clamping); in 18, sensations were more intense than with intact circulation and accompanied by pain, diminishing but not disappearing before end of stimulus; in 19, sensations of slight warmth only, indefinite after 100 seconds; in 20, slight warmth growing gradually and fading again, disappearing in about 82 seconds. Records 21 to 24 were obtained from 6 to 20 minutes after removal of the clamp during considerable hyperemia; the sensations were, with the exception of 24, only those of slight warmth. The room temperature (dry bulb) was approximately 21 C.

obtained, particularly in experiments 5 and 6 on the two cold days when there was a background of considerable vasoconstriction (skin pale and very cold). There appears to be a double curve, with a lengthening of the reaction time at rates of change of about 1 C. per second with direct stimulation, and at 0.6 to 0.7 C per second with reverse stimulation. It may be noted in table 2, experiment 6, that this lengthening of the reaction time was in reality even more consistent, since it depended on a stimulating temperature of about 35 C. on both surfaces. Cold spots were not mapped, but are likely to have been present. With rates of change above 2 C per second in experiment 7, the sensation was usually called "hot."

Attempts have been made to apply similar methods to data obtained when the depth of the end-organ may have been subdermal. The data are, however, variable and insufficient to warrant consideration here.

Temperature Change Necessary to Excite the End-Organ.—This value ($\Delta\ \Theta$) has been estimated as for cold. The mean values obtained in warm room conditions and the individual data calculated from experiments 5 and 6 are shown in figures 12 and 13. Those obtained with reverse stimulation are greater than those observed with direct stimulation, and the values are greater at the higher rates of change. As in the case of time values x, there is considerable variation from experiment to experiment at any given rate of change, and the curves relating the values to the maximum rate of change are complicated. The data show considerable scattering, with little evidence of grouping. For instance the data in the range of maximum rates of change between 0.7 and 0.89 C. per second, utilized in plotting the mean curves in figure 12, were sixteen and they varied between 0.08 and 1.12 C. (corresponding values for x —0.03 second and 1.21 seconds with a mean of 0.45 second). The data utilized in the same range for figure 13 (reverse stimulation) were only four in number, with extremes of 0.28 and 1.32 C. and a mean of 0.60 C. (corresponding extreme and mean values for x — 0.34 second, 2.43 seconds and 0.59 second). In only three cases of the whole series were negative values for x utilized and they are all included in the one group cited. (Positive values for $\Delta\ \Theta$ are possible even with negative values for x, since in the former corrections for galvanometer lag have been employed, and in the latter not.)

Stimuli of Long Duration.—Instances of stimuli of long duration are given in table 2, in which sensations diminished in intensity but persisted throughout contact, and several seconds after removal; in experiment 5, record 7, the rate of change per second during the last 30 seconds on the near surface was 0.015 C., and on the far surface 0.034 C. per second; in experiment 5, record 15, 0.003 C. on the near surface,

and 0.008 C. on the far surface, and in experiment 6, record 17, 0.003 C. per second on the far surface (near doubtful).

It should be noted that with a warm stimulus the temperature of the near surface remained considerably below that of the applicator (table 2) in contrast with the effect of cold stimuli. This appeared to depend on the differences in circulation rate, for with stasis (experiment 6, nos. 18, 19 and 20) the temperature of the applicator was reached. On the far surface the temperature of the applicator was not nearly reached either with intact circulation (experiment 6, record 15) or with stasis (experiment 6, record 20). If the stimulus employed was below the temperature of the blood, then the temperature of the applicator might be approached even without stasis. Thus, in another experiment a temperature of 36.5 C., applied to a fold (1.5 mm. thick), with initial temperatures of 29.1 C., near surface, and 29.15 C., far surface, increased

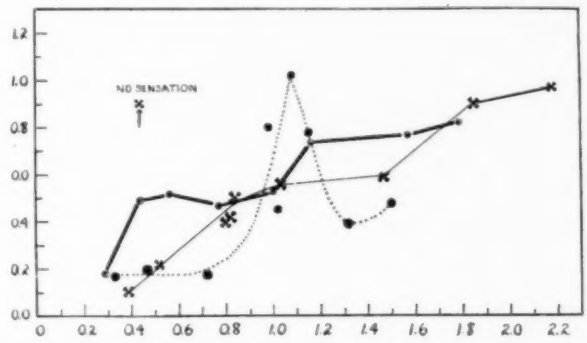


Fig. 12.—Relation of the values of $\Delta\ \Theta$ for warm stimulus to the maximal rate of change at depth d. The values are plotted as follows: experiment 5, subject 1, direct stimulation, crosses and solid line; experiment 6, subject 2, direct stimulation, solid circles and dotted line. The mean values are indicated as in figure 10. For room temperature, see the subscription to figure 10. The ordinates represent the value in degrees Centigrade; the abscissas, the maximal rate of change at depth d in degrees Centigrade per second.

these temperatures to 36.3 C. and 32.65 C. in 90 seconds, and to 36.4 and 32.65 C. in 120 seconds. A sensation of warmth developed in 0.75 second, decreased rapidly in intensity, increased again temporarily after 26, 43 and 60 seconds and disappeared practically completely, during the last 30 seconds.

Influence of Vascular Factors.—The evidence just given of the effect of stasis illustrates the complicating effects of the circulation carrying heat to the far surface, and assisting in thermal conduction (far surface warmed less in the presence of stasis), and yet distributing the heat over a large area and diminishing the temperature change on the near surface.

For the maximum temperature change at some distant point there may be an optimal circulation rate. The contrast in the temperatures reached with cold and warm stimuli indicates that the stimuli themselves alter the rate of circulation (Bazett, McGlone and Brocklehurst [6]). In experiment 6, after release of stasis there was a marked hyperemia with a slow rate of transmission, and the reaction time of sensation was extremely variable and often very long (Bazett, McGlone and Brocklehurst [6]).

As in the case of cold the position of the thermocouple might considerably affect the character of sensation; when it lay over a venous

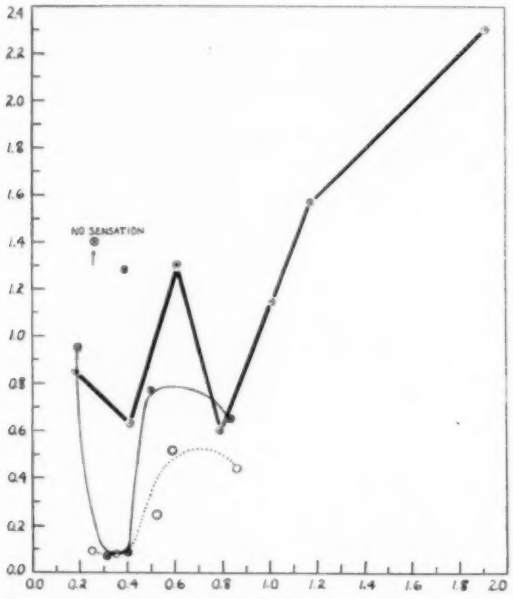


Fig. 13.—Relation of the values of $\Delta\ \Theta$ for warm stimulus to the maximal rate of change at depth d. The values are plotted as follows: Experiment 5, subject 1, indirect stimulation, crossed circle and solid line; experiment 6, subject 2, indirect stimulation, open circle and dotted line. The mean values are indicated as in figure 11. The ordinates and the abscissas are the same as in figure 12.

channel in which the flow appeared to be toward the warm spot, sensations were usually induced normally but faded rapidly, long before removal of the applicator. In one experiment, sensations were induced with about a normal latency but were of slight intensity even with stimuli over 40 C. (more than 12 C. above the surface). After a series of 8 stimuli, the thermocouple was moved to the other side of the warm spot and this resulted in intense sensations of much brisker onset, though the change also induced a slower development of the temperature

changes for corresponding stimuli. The latencies of sensation in the two series differed for similar stimuli but agreed when comparison was made on the basis of the rate of change.

Stasis was employed in two experiments. The rate of transmission of warmth was not consistently changed but was generally slowed. Sensations were at first brisk and definite but later of slow onset and decreased intensity (table 2, experiment 6).

After-Sensations of Warmth.—These after-sensations resembled those of cold, but were less frequent and less definite. They were sometimes referred by the subject to some other area. With long stimuli, after-sensations were usually not recorded but occasionally they appeared to be definite though slight and occurred when the temperatures on both surfaces were falling.

Occasionally after-sensations of warmth could be correlated with a secondary wave of increased temperature, or decreased rate of fall, occurring during the recovery period, but often no such correlation could be observed.

An after-sensation was once recorded approximately 8 seconds after the removal of a stimulus (applied on the reverse side) without any primary sensation. The latency corresponded with the maximum temperature change on the surface nearer the end-organ. The temperature changes were long maintained, seemingly indicating vasodilatation. The record is reproduced in figure 14.

Paradoxical Sensations of Warmth.—Such sensations were very rare in these experiments, regardless of the side stimulated, but mild stimuli only slightly below the surface temperature, which were often effective in the forearm, were only rarely employed. In a single experiment on subject 1, a direct stimulus of 16.5 C., applied to a surface at 25.85 C., gave a sensation called "hot" with a reaction time of 1.77 seconds, similar to that recorded for warmth with warm stimuli. On the surface stimulated, one warm spot surrounded by two cold spots at a distance of 2 and 3 mm. had been mapped. An applicator of 1.5 mm. was used and the temperature changes recorded were normal in type.

Comparison with Data Obtained in the Forearm.—The data obtained on the forearm previously published suggested that the end-organ for warmth was situated at a depth of about 0.6 mm.; these calculations were made on the assumption that $\Delta\,\Theta$ was constant. The data obtained in the prepuce indicate that neither the value of x nor of $\Delta\,\Theta$ is constant, but that the former is less variable than the latter. If the data are consequently recalculated on the assumption that $n + x$ is constant and may be represented by a single value y, the calculated depth of the end-organ determined varies according to the data grouped. By the use of

median values for reaction time, d is 0.75, 0.35 or 0.13 mm.; by the use of the mean values it is 0.30, 0.40 or 0.51 mm. The mean of both groups is 0.4 mm., the same value as that previously calculated. A comparison of the values obtained in cold rooms with those obtained in warm rooms is likely to be least in error; this would give a depth between 0.30 and 0.75 mm. In spite of the wide range of the possible calculations, the former estimate of 0.4 to 0.6 mm. appears most probable and agrees well with the value of 0.56 mm. obtained by Endres (1930).

The depth in the forearm is therefore assumed to be 0.5 mm. in analyzing our previous data. The curves recorded in figure 7 of the earlier paper are redrawn on a uniform scale (fig. 15) with corrections

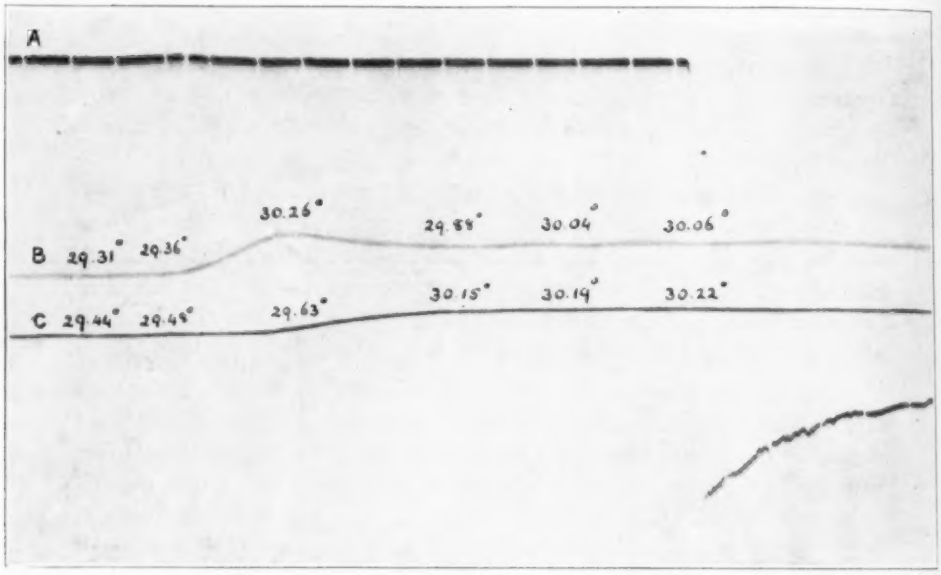


Fig. 14.—Record of experiment 7, subject 2, to show after-sensation with an absence of primary sensation. See the text. The stimulating temperature, doubtful-starting at 41 C. (stimulus, + 11.70) and falling, was applied for 2.87 seconds to the proximal surface. *A* is a subjective record of sensation, duration of downstroke, "mild warmth of gradual onset"; the interruptions indicate time in seconds. *B* is a record of temperature changes of the proximal surface of a dorsal fold. *C* is a record of the temperature changes of the distal surface. The warm spot is nearer the distal surface.

as in figure 8. Rapidly reversing gradients may be distinguished and these may be more clearly seen in figure 16, where the data are plotted on a spatial gradient basis. The curves have been estimated as those of cold, except that after the warm stimulus cooling appears to occur not only at the surface but also as the result of the entrance of cooled blood from the surrounding tissue. It is of interest to estimate, as far

as this is possible, the temperature characteristics at the time of onset and fading of sensation, as in the case of cold. The onset of stimulation occurred 0.77 second after contact, when the temperature change should be commencing at about 0.6 mm.; at 0.5 mm. the time value x would be 0.13 second and $\Delta\ \Theta$, 0.1 C. for an estimated maximum rate of change of about 1 C. per second, values not particularly at variance with those obtained in the prepuce. Stimulation commenced to fade 0.36 second after removal, when the temperature at 0.5 mm. depth should still have been increasing, but more slowly than previously; it had disappeared after 1.96 seconds [7a] when the maximum temperature change should have been reached at about 0.75 mm. depth

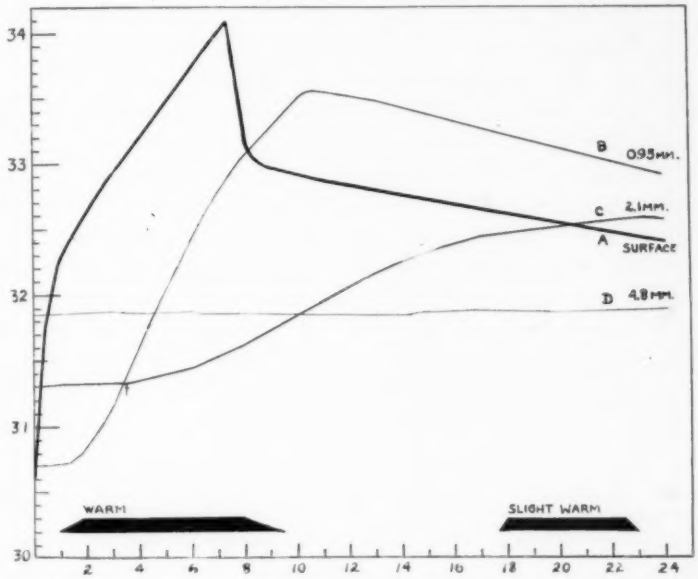


Fig. 15.—Corrected curves from the record of the changes of temperature on the surface (*A*), and at depths of 0.95 (*B*), 2.1 (*C*) and 4.8 mm. (*D*) in the forearm. The stimulating temperature was 40.8 C. (stimulus, +12.2 C.); duration, 7.4 seconds. The sensations are as noted. See the text for description.

and when the temperature at 0.5 mm. depth should have been falling (maximum temperatures at this depth probably at about 0.75 second after removal). The slight after-sensation was associated with a spatial gradient of the type indicated in figure 16, curve 7.

Some evidence that spatial gradients may be important has been obtained in the forearm with lateral stimulation. An applicator of 1.5 mm. diameter at 41.6 C., applied about 1 mm. lateral to a warm

7a. These three time values have been corrected by substracting 0.14 second for nervous processes.

spot, gave changes of temperature which started almost simultaneously at two depths—change at 0.65 mm. from 33.95 to 35.7 C. in 7.65 seconds (maximum rate of change, 0.29 C. per second) and at 1.6 mm. from 34.25 to 35.5 C. in 8.25 seconds (maximum rate of change, 0.285 C. per second). There was no sensation in spite of this relatively high rate of change. A stimulus of 42 C. applied over the spot gave a sensation "hot," but the estimated rate of change at 0.5 mm. was then increased to about 0.8 C. per second.

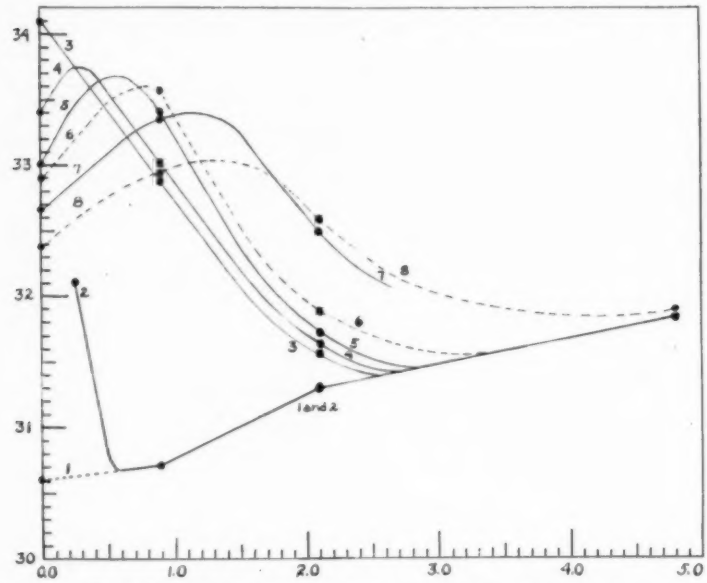


Fig. 16.—Probable spatial gradients in the tissue during the temperature changes shown in figure 15 at (*1*) fore-period, (*2*) onset of sensation, 0.78 second after the stimulus was applied, (*3*) end of the stimulus, 7.41 seconds, (*4*) 0.46 second after the end of the stimulus, "sensation commencing to fade," (*5*) 1.6 second after the end of the stimulus and 0.5 second before the end of the sensation, (*6*) 3.1 seconds after the end of the stimulus and 1 second after the end of the primary sensation, (*7*) 12.2 seconds after the end of the stimulus and at the onset of the after-sensation of warmth, (*8*) 19 seconds after the end of the stimulus. The solid lines indicate gradients during sensation; the broken lines, gradients during the absence of sensation. The ordinates represent temperatures; the abscissas, depths in millimeters.

COMMENT

The results obtained may be compared with previous theories and the numerous data already in the literature. In making comparisons it must be remembered that previous workers have recorded the tempera-

ture of the stimulus and have assumed that the surface attains this temperature. In the experiments here reported, actual measurements show much smaller temperature changes at the applicator-skin boundary. The thermocouple is, however, embedded in a groove in the skin during application and may therefore in reality record the temperature changes occurring at some slight depth below the surface; even so, better correlation is to be expected and is found between sensation and such records than with the mere temperature of the applicator. In many cases anomalous temperature changes may be recorded, but the sensations may also show corresponding anomalies.

Number and Character of End-Organs Involved.—Arguments have been advanced in a previous paper that the end-organs involved in the sensations of cold and warmth are those of Krause and Ruffini, respectively. The suggestions of Head and Rivers (Head [8]) that there are different kinds of end-organs sensitive to temperature, and of Gertz [9] that temperature sensations of deep origin may be induced, raise the question whether the results obtained depend on stimulation of only two types of end-organ. In the case of warmth there is histologic evidence that Ruffini's end-organ may occur either in the dermis or subdermis in the prepuce, as in other parts of the body; Sfameni [10] reported the presence of Ruffini end-organs in periosteum; probably, therefore, deep sensations of warmth occur, but in the prepuce only subdermal end-organs could complicate the issue, and these should be recognizable physiologically in the thin fold employed. Radiation to the skin often gave slight sensations of diffuse warmth, which may have depended on some other type of end-organ, but these sensations were usually not confused with a more definite sensation of warmth induced soon after contact of the applicator. The data obtained may therefore be considered as entirely dependent on warm spots, though the existence of other end-organs is not necessarily excluded. The complicated curves representing the threshold temperature change necessary to produce sensations of warmth might be interpreted as being dependent on stimulation of several end-organs, but it will be seen that vascular adjustments and some interference of sensations of warmth with those of paradoxical cold might account for the observed results, and that the assumption of other end-organs as a factor in their production is unwarranted.

In the case of cold, subject 2 had a large area free of cold spots and no sensation of cold whatever could be induced in this area with

8. Head, Henry: Studies in Neurology, London, Oxford University Press, 1920, pp. 63 and 316.

9. Gertz: Ztschr. f. Psychol. u. Physiol. d. Sinnesorg **52**:1 and 105, 1921.

10. Sfameni: Monitore zool. ital. **12**:313, 1901.

applicators of 0.2 sq. cm. surface. There was never any evidence in the prepuce of subdermal end-organs sensitive to cold, and a single group of end-organs must have been involved.

Weber's Hypothesis.—If this were correct, the time value (x) necessary to induce sensation should be a function of the rate of change regardless of the surface stimulated. In the case of cold, the data definitely contraindicate any such relationship, and the differences observed exceed probable experimental errors. Maintained sensations of cold reported by some subjects and maintained sensations of warmth reported by all subjects, when the rate of temperature change has become extremely small or nil, are also not explicable on this theory except on a basis of rotation between different end-organs. Recent observations of Lewis [11] suggest rhythmic variations in vasomotor tone on exposure to cold, and still earlier Gertz [9] had already invoked the presence of such changes to explain rhythmic variations in sensation, but there is no justification in attributing all prolonged sensations to rotation on such indirect evidence.

The data obtained on the prepuce also suggest, though less definitely, that for warmth the time value x does not vary simply with the rate of change but also with the surface stimulated. Weber's hypothesis appears therefore inadequate.

Hering's Hypothesis.—If this theory were correct, sensations should be induced when the temperature had been altered through a definite threshold value, regardless of the surface stimulated, but in the case of cold the value with reverse stimulation is three times that with direct. No errors in the estimation of depth of the end-organ or of calculation of the change could account for such a large difference, and the apparent constancy of the threshold change in stimulation of cold spots from the nearer surface presumably has some other explanation. Sensations of long duration are also hard to explain, and the ultimate occurrence of adaptation is most readily attributable to changes in blood temperature, as in Ebbecke's theory. Also in the case of warmth the threshold temperature change $\Delta\,\Theta$ appears to vary according to the surface stimulated, and maintained sensations of indefinite duration may be produced by high temperatures, while adaptation occurs to more moderate stimuli. Gertz [9] found that full adaptation to warmth did not occur in the finger with temperatures above 36 C. (approximately the temperature of the blood supplying the fingers), but with immersion of the whole forearm in water it may be observed with temperatures as high as 37 C.[12] In the

11. Lewis, T.: Heart **15**:177, 1930.

12. Bazett, H. C., and McGlone, B.: Studies in Sensation: III. A Chemical Factor in the Stimulation of End-Organ Giving Temperature Sensations, Arch. Neurol. & Psychiat., to be published.

finger, exposure to still higher temperatures (e. g., 42 C.) gave, however, according to Gertz, a partial adaptation in that water at a lower temperature (e. g., 40 C.) might no longer give thermal sensations ("wirkliche Adaptationstemperatur"). He found that the difference between the temperature of exposure and effective adaptation varied with the degree of hyperemia induced. Such results appear due, as Gertz supposed, to the degree of alteration of temperature in the inflowing blood, and the differences he observed between the temperature of the water bath used and the effective adaptation attained are very similar to those observed between surface and subcutaneous temperatures on exposure to heat (Bazett and Sribyatta,[13] fig. 7).

Adaptation is consequently most readily explained as the result of actual changes in the blood temperature, so that Hering's theory is not supported either as to the essential stimulus being the change of temperature in the end-organ or in regard to the mechanism of adaptation.

Ebbecke's Hypothesis.—Ebbecke [3] considered that temperature sensations were induced when spatial thermal gradients were altered, and in his classic experiments he emphasized the importance of the circulatory factor. He wrote:

> Eine Kältempfindung kommt zustande wenn warmes Blut in kalte Haut strömt. Nicht das Steigen oder Sinken der Hauttemperatur—ist für die Empfindung entscheidend, . . . sondern die Differenz zwischen den zu beiden Seiten des Endapparats bestehenden Temperaturen . . . die normalerweise durch das Blut unterhalten wird. (A sensation of cold is produced when warm blood streams into the cold skin. Not the increase or decrease in the cutaneous temperature which is normally maintained by the blood . . . determine the sensation, . . . but the difference between the temperature existing at the two sides of the end-apparatus. . . .)

For the importance of the circulatory factor there is much additional evidence. Waterson [14] noted that the number of cold spots that could be identified were increased when the arm was blanched by being elevated and vice versa, and sensations of warmth were found to be intensified in inflammatory hyperemia. Gertz [9] noted that adaptation to cold was upset if any change in the circulatory condition was induced, and described the "wirkliche Adaptationstemperatur" to hot stimuli, to which reference has already been made.

More distal areas of skin may be adapted to lower temperature than those more proximal (von Frey [15]). The skin of the finger may be adapted till 16 C. no longer feels cold (Gertz [9]), and with stasis temperatures as low as 12 C. may cease to feel cold to the finger (Goldscheider

13. Bazett, H. C., and Sribyatta, L.: Am. J. Physiol. **86**:565, 1928.
14. Waterson, D.: Rep. St. Andrew's Inst. Clin. Research **1**:183, 1922.
15. von Frey, M.: Ergebn. d. Physiol. **9**:351, 1910.

and Hahn [16]). Total immersion of the forearm or local applications of cold to a spot ceased to give cold sensations after some time in the experiments here reported in subject 1, but continued to do so in subject 2; there is much evidence that subject 1 showed a greater vasoconstriction to cold than subject 2 (compare fig. 9 of Bazett and McGlone [7]). Stasis greatly interferes with reverse stimulation of cold in the prepuce, even though the temperature changes may be effectively transmitted.

During stasis, normal sensations are induced with spot-stimulation in the forearm, but after-sensations are no longer in evidence (Bazett, McGlone and Brocklehurst [6]); such results have been less definite in the prepuce where complete stasis is difficult to ensure. After-sensations in the prepuce may often be correlated with secondary temperature changes, which appear in turn to depend on temporary alteration in the circulation. If thermocouples are placed on the surface so that when pressed into the skin they may interfere with the circulation (particularly if they lie distal to the end-organ, where they might interfere with venous flow toward it) they may greatly interfere with the production and maintenance of cold and warm sensations; a slight change in the position of the thermocouple can entirely remove this effect. Slight sensations of warmth and cold may be induced if areas distal (according to venous paths) to the most sensitive spots are stimulated. The latencies of both cold and warm sensations vary with the vascular condition, and vascular dilatation appears to raise considerably the threshold stimulus for cold.

All such observations are readily explained if the circulation plays an essential rôle in the normal stimulation of temperature sensations, and the fact that sensations may be induced during stasis does not exclude blood contained in the vessels as an essential factor.

On the other hand, Ebbecke's hypothesis cannot be accepted without modification; he wrote:

> Kälteempfindung wird ausgelöst durch eine Temperaturdifferenz in der Hautschicht an der Grenze von Epidermis und Cutis, Wärmeempfindung durch eine Temperaturdifferenz in der Hautschicht an der Grenze von Cutis und Subcutis. (Sensation of cold is produced by a temperature difference in the cutaneous layer at the border of the epidermis and cutis, sensation of warmth by a temperature difference in the cutaneous layer at the border of the cutis and subcutis.)

If this were true, reverse stimulation with cold of a prepuce fold, which contained both warm and cold spots, should produce a paradoxical sensation of warmth, and such phenomena have been conspicuously absent.

Modified Ebbecke Hypotheses.—Possible modifications would be: (*a*) the production of tissue-blood vessel thermal gradients at depths of

16. Goldscheider and Hahn: Arch. f. d. ges. Physiol. **206**:337, 1924.

from 0.1 to 0.3 mm. in the prepuce, with stimulation occurring when the gradient is in a definite direction or regardless of the direction of the gradient; (*b*) production of arterial-venous thermal gradients with similar possibilities as to direction; (*c*) induction of sensation as the result of either cooling or warming of the blood or both, if it occurred in the neighborhood of the end-organ, whether the temperature change occurred as the result of a change in temperature of the tissue as a whole or as the result of the flow of blood across a thermal gradient. These various alternatives may be considered in relation to sensations of cold and warmth separately. Hypothesis (*b*) will receive no consideration at present; though it is a possibility, it could be established only on histologic evidence.

Cold: There is much evidence that might equally support either the (*a*) or (*c*) modifications. Ruffini [17] described Krause's end-bulbs lying in the fingers close to a capillary loop, and they appear in the prepuce to lie close to the superficial venous plexus. With direct stimulation and under normal circulatory conditions the threshold change $\Delta\ \Theta$ might be expected to be relatively constant on either theory, (*a*) or (*c*), since the blood, of high thermal capacity and circulating, should show much less temperature change than the tissues. Somewhat in favor of (*a*) would be the apparent slight increase in $\Delta\ \Theta$ with increasing strengths of stimulus (partial cooling of blood stream); in favor of (*c*), the increase in threshold with hyperemia, which might be expected to facilitate the induction of a tissue blood vessel gradient and therefore on hypothesis (*a*) to facilitate stimulation.

The greater value of $\Delta\ \Theta$ on reverse stimulation and an increase in $\Delta\ \Theta$ with increasing strength of stimulus would be accounted for by either (*a*) or (*c*), since some cooling of the blood would occur before it reached the end-organ. The group of data in which $\Delta\ \Theta$ remained relatively constant even in reverse stimulation could only be accounted for on either theory by a chance supply of blood to the end-organ along a channel little exposed to the thermal changes, but this would leave the raised level of the threshold unaccounted for. The difficulty experienced in inducing reverse stimulation of cold spots during stasis is more in favor of (*a*).

The occurrence of paradoxical sensations of cold with hot stimuli (in preliminary experiments without thermocouples) indicates that the direction of the gradient according to (*a*) of the local change in blood temperature according to (*c*) is immaterial. Altrutz [18] showed that the latency of such sensations is very long (0.745 second). The normal blood tissue gradient would, however, have to be reversed before warm

17. Ruffini, G.: Rev. gén. d'histol. **1**:425, 1905.

18. Altrutz: Ztschr. f. Psychol. **47**:161 and 241, 1908.

stimuli became effective on either hypothesis (*a*) or (*c*), and in addition a warm stimulus might produce vasodilatation even during the process of stimulation, and possibly this might help to exaggerate the reaction time.

The data obtained in the forearm could be explained on either theory if after-sensations are produced in other end-organs at a distance; if caused partly at the end-organ originally stimulated, after-sensations would have to depend on blood entering the cooled tissue at a faster rate, so that phenomena of thermal gradients or local cooling of the blood were intensified. The data reported by von Frey [19] seem to be conclusive that after-sensations are caused by lateral spread to other end-organs, and either hypothesis (*a*) or (*c*) would thus account equally well for the phenomena.

The frequent apparent correlation of the after-sensations in the prepuce with demonstrable secondary waves of lowered temperature might well depend on conduction of the cooling along venous channels, which might then secondarily affect the end-organs lying superficial to them; such a correlation could be accounted for by either hypothesis (*a*) or (*c*).

Adaptation to cold would be readily explained by either (*a*) or (*c*); as the lowered temperature progressed inward, the blood would be cooled before reaching the end-organ and neither marked thermal gradients nor local cooling of blood would be much in evidence. The greater the vasoconstriction, the more readily would this occur, and any diminution in vasoconstriction should upset equilibrium and cause recurrence of sensations.

Warmth: Ruffini [17] described the end-organs that bear his name as being surrounded by a rich capillary network, the branches of which, however, do not penetrate the end-organ. These vessels are apparently regarded as of arterial origin. On histologic grounds it is therefore difficult to believe that the temperature of the end-organ could change much more rapidly than that of the blood surrounding it, and the structure appears fitted to detect changes in blood temperature in the neighborhood of the end-organ or of a blood end-organ thermal gradient. If the end-organs lie close to venous channels, as appears to be the case in the prepuce, possibly such veins lie in proximity to but unconnected with the vessels supplying the end-organ, and cause alterations in temperature of the entering arterial blood.

The data may for the most part be explained on either the (*a*) or (*c*) modification of Ebbecke's theory, though the causation of the complicated curves must first be considered. The sudden increase in the latency of sensation with rates of change of about 1 C. per second

19. von Frey, M.: Am. J. Physiol. **94**:505, 1930.

(direct) and 0.6 C. per second (reverse) occurs when the rate of change at the level of end-organs for cold, both with direct and indirect stimulation, is at least 0.9 C. per second, a rate which might be expected to induce paradoxical sensations of cold. The lengthening of reaction time is similar to that found when two sensory mechanisms interfere and when one has some inhibiting effect on the other (compare the curves given by Creed and Granit,[20] illustrating interference of after-images in the retina). In favor of such an explanation is the character of the signals, which showed no evidence of dilemma on the part of the subject with direct stimulation and rates of change at the cold spot level of less than 0.8 C. per second, but which often gave evidence of subconscious hesitation with stronger stimuli. Since the latency of paradoxical cold is long (Altrutz), the two sensations might be induced with similar latencies. Simultaneous cold and warm stimulation has long been recognized as giving rise to "hot" sensations, and further proof of this has recently been advanced by Burnett and Dallenbach,[21] but evidence of interference of the two sensations may also be found in the literature; Hahn[22] stimulated the skin with interlocking coils through which cold and warm water were circulated simultaneously; he found that stimulation of cold spots after induction of a warm sensasation produced a hot sensation, but that simultaneous induction of the two sensations gave rivalry with alternate sensations of cold and warmth.

Warm stimuli themselves probably cause vasodilatation (Bazett, McGlone and Brocklehurst[6]) and such vascular changes might readily affect the threshold value of the stimulus on either hypothesis (*a*) or (*c*). One might therefore explain the complicated curves given for x and $\Delta\ \Theta$ in the case of warmth by assuming that at rates of change less than from 0.1 to 0.2 C. per second, no sensation from a single Ruffini end-organ is possible; that with greater rates of change, x is rapidly reduced from infinity to a low value of less than 0.1 second until interference with paradoxical sensations of cold occurs, when it becomes again much lengthened; that on further increasing the strength of stimulus, x is again reduced but that vasodilatation, caused by the stimulus itself, ultimately counteracts the effect of the stronger stimulus, so that x is again lengthened. That vasodilatation may have some such effect has already been demonstrated in the forearm (Bazett, McGlone and Brocklehurst[6]).

The values of $\Delta\ \Theta$ show similar variations, which may receive the same explanation; there is also a general tendency for $\Delta\ \Theta$ to increase with increasing strength of stimulus. The marked occurrence of these

20. Creed, R. S., and Granit, R.: J. Physiol. **66**:281, 1928.
21. Burnett, N. C., and Dallenbach, K. M.: Am. J. Psychol. **38**:418, 1927.
22. Hahn, H.: Arch. f. d. ges. Psychol. **65**:41, 1928.

phenomena of interference in the prepuce, though so little in evidence in the results of other workers in other areas, might depend on the initial considerable vasoconstriction in the prepuce as the result of exposure and consequent cooling; at any rate, the phenomena were much more in evidence in the two experiments performed in an especially cold room. Though Piéron,[23] in measurements of reaction times, found no such phenomenon, it may be seen to some extent in the data obtained by Altrutz.[18] He found the reaction time to warmth in himself to be 0.38 second, but with hot stimuli the latency was 0.795 second even though no preliminary sensation of warmth was induced. With the hot stimulus increased to 46.5 C., the latency was reduced to 0.517 second, but with a further increase to 50 C. it was again lengthened to 0.544 second. In the prepuce, hot sensations were only recorded when the rate of change at 0.1 mm. depth exceeded 2 C. per second; occasionally, the first sensation was heat; more commonly the initial sensation was warmth.

The complicated relationships of the latency of sensations of warmth and of the amount of thermal change necessary according to the strength of the stimulus seem therefore to be explicable on the basis of interference between sensations of cold and warmth and of vasodilatation modifying the ease with which the stimuli become effective.

That the value of $\Delta\,\Theta$ is greater with reverse than with direct stimulation, and that with both directions of stimulation its value increases with increasing strength of stimulus is in harmony with either the (*a*) or (*c*) modified hypothesis. That the contrasts between the two surfaces, both in absolute value and in rate of increase with varying stimulus, are less marked than in the case of cold is similarly in harmony with both modifications, since the variations in the distance between applicator and end-organ and consequent exposure of vascular channels are less in the case of warmth.

Hyperemia lengthens the latency for warm sensations as well as those for cold (see data obtained in the forearm); this is more readily explicable by (*c*) than by (*a*).

Paradoxical sensations of warmth are not readily obtained, and when observed are described as induced by mild rather than by extreme cold stimuli. They have been employed by Ebbecke as evidence that in the end-organ for warmth also the direction of change or orientation of the thermal gradient is immaterial. Such an explanation is possible if exposure to extreme cold causes vasoconstriction involving the vessels supplying the Ruffini end-organs, and so interferes with the production of sensation. An alternative explanation, and one perhaps even more probable, is that these end-organs are in reality only excited if the blood is warmer than the end-organ according to theory (*a*), or if the blood

23. Piéron, H.: Année psychol. **20**:1, 1914.

is warmed in the neighborhood of the end-organ according to theory (*c*), and not vice versa. The slight sensations of paradoxical warmth which may be generated by mildly cool stimuli would then be grouped with those resulting from mechanical stimuli. Head,[8] for instance, warned against the "tendency to call neutral stimuli warm, which is so frequently a source of confusion with thermal tests." Hacker [24] thought that such paradoxical sensations had a mechanical origin, since he noted that they might be induced by the application of a temperator but not by a change in the temperature of the circulating water, that they could be caused by applicators of 0.5 sq. cm. area, but not by pressure applied with hairs. But such mechanical stimulation may in reality be thermal, for it has been shown that the venous return may be readily interfered with by pressure, and a consequent sudden rise of temperature be induced at a depth (Bazett, McGlone and Brocklehurst [6]). The contrast observed by Hacker between hairs and applicators of larger surface as well as the ineffectiveness of really cold stimuli would thus receive a ready explanation. It seems probable that end-organs for warmth respond only either to a rise of temperature in their neighborhood or to a gradient in which the blood is warmer than the end-organ.

After-sensations are often indefinite; they might be explained by lateral spread as in the case of cold, particularly if they depend on stimulation of subdermal end-organs. The occurrence of after-sensations of warmth in recovery from a cold stimulus under certain conditions (von Frey [19]) might be explained by hypothesis (*a*) or (*c*).

Lateral stimulation of a warm spot appears to be difficult in the forearm under conditions when the rate of change of temperature is similar at two different depths. This is somewhat in favor of the (*a*) hypothesis. Analysis of the genesis and fading of sensations in the forearm is inconclusive; it is not in antagonism with either hypothesis (*a*) or (*c*). Maintained sensations with hot stimuli are more difficult to explain by hypothesis (*a*), since a maintained thermal gradient between the end-organ and the surrounding capillary loops is hard to imagine.

Prolonged sensations of mild warmth may occur after cold bathing ("warm glow"). A similar mild, and apparently peripheral, sensation of warmth may be experienced continuously in a warm room. Both conditions are probably associated with low thermal gradients in the subcutaneous tissues, and the latter at any rate with high gradients in the superficial layers of the dermis. Both such sensations could therefore be explained on hypothesis (*a*), but only the first on hypothesis (*c*), if dermal end-organs are involved. Since little is known of the arrangement of Ruffini end-organs in the subcutaneous tissue, this evidence is inconclusive.

---

24. Hacker, F.: Ztschr. f. Biol. **61**:231, 1913.

Mechanism of Stimulation.—Considerable emphasis has been placed in this discussion on the importance of the blood stream in stimulation, apart from the effect of the circulation on the development of thermal gradients. The emphasis has been so placed owing to the striking capacity of surface thermocouples to obliterate sensations without preventing the temperature changes, a phenomenon tentatively ascribed to a local ischemia. If, however, this view be correct, adaptation would be expected to develop more rapidly during stasis; Gertz [9] reported that this is not the case. While therefore the data appear to favor a hypothesis of the Ebbecke type, it has not proved possible to advance any entirely satisfactory modification, though, on the whole, modification (*c*) perhaps agrees best with the observed data. It is, however, difficult to see how such local temperature changes in the blood, or local gradients, could act as a stimulus to the end-organ, and the whole question is complicated still further by some chemical process. For, in experiments designed to test the temperature changes accompanying sensations induced by release of stasis, it has been found that release of stasis in a limb immersed in water at blood temperature gives a marked sensation of warmth, even though the blood enters tissue of the same temperature, and produces no measurable thermal gradient nor any change in temperature. Apparently blood previously stagnant in muscle tissue can without thermal changes produce sensations of warmth when circulating through the dermis. The actual stimulus would therefore appear to be a chemical, not a thermal, gradient.[12]

Chemical gradients of some such type might stimulate an end-organ by variations in hydrogen ion concentration. It is difficult to see how local warming or cooling of blood could be effective, unless during the change of temperature some chemical change occurred in the blood, which might later be neutralized by contact with tissues. Though the Weber hypothesis of the importance of $\frac{d\Theta}{dt}$ is not supported as far as changes in temperature in the tissues at the depth of the end-organs are concerned, a hypothesis of this type might be valid if applied to changes in temperature or in chemical composition of blood. For the present the subject must be left vague; neither modification of Ebbecke's hypothesis appears entirely satisfactory, but if thermal alterations cause secondary chemical changes before sensation is induced, the possible variables are hard to estimate.

CONCLUSIONS

1. It is assumed that the correlation indicated in a previous paper between the distribution of Krause and Ruffini end-organs and spots sensitive to cold and warmth establishes these end-organs as those concerned in these sensations. On this basis the temperature changes involved in stimulation are discussed.

2. The data are considered to be inconsistent with either the Weber or the Hering hypothesis of the generation of temperature sensations. They are also inconsistent with Ebbecke's theory, so far as it depends on contrasts between dermal and subdermal spatial gradients.

3. Sensations are considered to be elicited either as the result of spatial gradients between blood vessels and tissues in the neighborhood of the end-organs, or as the result of temperature changes in blood. The latter might be induced either by temperature changes involving the whole area or by blood flow in a vessel from one area to another at a different temperature. Difficulties that arise in explaining the data on either of these two hypotheses are discussed.

NERVE DEGENERATION ACCOMPANYING EXPERIMENTAL POLIOMYELITIS

II. A HISTOLOGIC AND FUNCTIONAL ANALYSIS OF NORMAL SOMATIC AND AUTONOMIC NERVES OF THE MONKEY

GEORGE H. BISHOP, PH.D.

PETER HEINBECKER, M.D.

AND

JAMES L. O'LEARY, M.D.

ST. LOUIS

The object of this research was to obtain data on the physiologic properties of nerves from normal monkeys, first, for comparison with nerves from monkeys afflicted with poliomyelitis, and second, for comparison with the nerves from other normal species, on which a considerable amount of data is being accumulated.

METHODS

The animals employed were adult normal Macacus rhesus from stocks supplying poliomyelitis researches. Data were obtained by photographically recording the action potentials of freshly excised nerves, employing the cathode-ray oscillograph and a four-stage resistance-coupled amplifier, the whole having a sensitivity of 200 mm. per millivolt and no appreciable inertia. The nerves were removed under light ether anesthesia and when the data were not recorded immediately were kept in iced Ringer's solution, where they would remain approximately normal for from one to three hours at least. They were placed for experimentation in a water-jacketed thermostat at 37 C., mounted on Ringer-filled mercurous chloride electrodes for stimulation and recording, and stimulated by condenser shocks, with the general technic for obviating distortion by the stimulating currents as discussed elsewhere (Bishop[1]). The nerves were then fixed and stained in 1 per cent osmic acid for from four to forty-eight hours. They were embedded in paraffin or doubly embedded in celloidin and paraffin and cut from 3 to 5 microns in thickness.

Because the cathode-ray oscillograph is a new type of recording mechanism, a brief description is inserted here. For those interested, fuller descriptions can be found in the articles of Gasser, Erlanger, Bishop and Heinbecker. The cathode-ray oscillograph is a thermionic vacuum tube of a type in which a beam of

---

Submitted for publication, Oct. 5, 1931.

From the Departments of Ophthalmology, Surgery and Anatomy, Washington University School of Medicine.

Made possible by a grant made by the International Committee for the Study of Infantile Paralysis to the Department of Anatomy and by a grant made by the Rockefeller Foundation to Washington University for research in science.

1. Bishop, G. H.: The Form of the Record of the Action Potential of Vertebrate Nerve at the Stimulated Region, Am. J. Physiol. **82**:462, 1927.

electrons is projected onto a fluorescent screen painted on the end of the tube. The electron beam on its course to the screen passes between two pairs of plates set at right angles to each other. A potential applied to the vertical pair of plates deflects the beam in the horizontal plane, and the focused electrons move across the screen as a line. The speed of this movement across the screen can be controlled and measured. The line serves the same purpose as a base line in a kymographic record. By means of a circuit breaker or double key a stimulus can be synchronized with any point in this deflection. This stimulus, together with the resultant action potential from the nerve, is applied to the other pair of plates, which causes a deflection of the electron beams at right angles to the base line. A visible standing-wave picture results that can be exactly repeated as frequently as the tissue will respond, and can be recorded photographically.

It is known that when a nerve fiber becomes active there is a potential change at the site of activity. This activity is propagated along the nerve fiber. Recording electrodes placed on the nerve will serve to convey the potential change of activity to the amplifier-oscillograph combination and cause a deflection of the electron beam. As different fibers within a complex nerve trunk have different conduction rates, it is readily understood that when a group of fibers is activated by an electrical stimulus and the activity is propagated along the axons, those in which the propagation is most rapid will produce a change in the recording electrodes before the more slowly conducting axons. As a consequence, from a complex nerve trunk the complete conducted action potential record will consist of a series of waves the thresholds, time relations and amplitudes of which, under specified experimental conditions, give significant physiologic data as to the fiber content of the nerve and the state of activity of its fibers.

It was found previously that vertebrate nerves in general contain four types of axons, which can be differentiated by their action potentials (Bishop and Heinbecker [2]). The first two types predominate in general in somatic nerves, and are characterized by time functions that are relatively brief; that is, their conduction rates are fast, the duration of potential activity is short, and their absolutely refractory periods and chronaxia values are small. The last two types, on the contrary, including the fibers of the autonomic system, are slow and sluggish in all their activities. Autonomic fibers coursing in somatic trunks can there be recognized by their potentials, although it is not certain that all fibers with these potentials are efferent. Also afferent fibers of somatic type run in visceral nerves, and can there be recognized also by their potentials. In fact, the second of the first two types usually occurs in visceral nerves, and may be relatively numerous there where they appear to include the typically visceral afferents.

Of the functions enumerated, the conduction rate is perhaps the least differential, and in visceral nerves the second and third groups may have conduction rates so little different, although differing abruptly in other respects, that their potentials partly overlap at ordinary distances of conduction. For this reason their potential records sometimes

2. Bishop, G. H., and Heinbecker, P.: Differentiation of Axon Types in Visceral Nerves by Means of the Potential Record, Am. J. Physiol. **94**:170, 1930.

appear as one complex wave, preceded by the distinct group of waves of the first type of axons, and followed by another distinct group of waves due to the fourth type. Functionally, however, the second group closely resembles the first, and the third closely resembles the fourth, the sharp line of differentiation falling between the second and third

Properties of Monkey Nerves

Nerve	Conduction Distance, Mm.	Thresholds, Voltage and Capacity*				Conduction Rates, Meters per Second				Absolutely Refractory Periods, Sigmas			
		I	II	III	IV	I	II	III	IV	I	II	III	IV
June 18, 1930													
Splenic	90	.....	.....	31.0 C_1	55.0 C_4	....	....	6.0	0.5	...	...	...	...
Lumbar sensory root 1	55	1.5 C_1	3.0 C_4	4.5 C_4	100.0 C_4	28.0	15.0	6.2	0.5	1.6	...	4.8	...
Lumbar sensory root 2		All potentials present including the fourth											
Lumbar motor root 1†	44	1.5 C_1	.....	.....	.....	30.0	....	...	...	...	...	...	...
Lumbar motor root 2		First potential wave present; no fourth elicited											
Cervical sympathetic	33	.....	7.5 C_1	31.5 C_1	7.5 C_4	....	11.0	2.9	0.6	...	1.9	...	...
Genitofemoral‡	38	3.0 C_1	.....	.....	.....	26.0	....	...	...	...	...	...	...
Vagus	20	.....	3.0 C_1	7.5 C_1	45.0 C_4	....	16.0	3.6	0.5	...	...	...	...
Jan. 13, 1931													
Phrenic‡	27	1.5 C_1	.....	.....	.....	16.0	....	...	...	...	...	...	...
Femoral	37	3.0 C_2	16.5 C_2	?	52.5 C_4	28.0	9.3	...	0.4	...	...	...	...
Vagus	40	4.0 C_2	7.5 C_2	67.0 C_2	50.0 C_4	26.7	17.4	2.3	0.4	...	...	...	...
Saphenous	44	1.5 C_1	4.5 C_1	12.0 C_1	90.0 C_1	27.5	17.6	2.0	0.5	...	...	...	...
January 21													
Radial	35	4.5 C_1	27.0 C_1	?	135.0 C_4	38.5	17.0	?	0.5	1.0	2.0	...	4.5
Femoral	35	6.0 C_1	25.0 C_1	157.0 C_1	157.0 C_4	27.0	10.3	7.4	0.5	1.0	1.4	4.0	4.5#
January 22													
Sciatic	72	3.0 C	16.5 C_1	40.0 C_1	?	28.0	14.4	8.4	?	...	...	...	...
Radial	30	4.5 C_1	15.0 C_1	35.0 C_1	60.0 C_4	35.0	14.0	6.5	0.45	...	...	...	...
Median cutaneous forearm	47	4.0 C_1	10.5 C_1	15.0 C	30.5 C_4	25.0	12.0	5.5	0.4	0.84	...	...	5.0
Femoral	39	3.0 C_1	15.0 C_1	28.0 C_1	40.0 C_4	23.0	10.0	5.2	0.3	...	...	...	...
Lumbar motor root		No fourth potential present											
Lumbar sensory root		Fourth potential present											

* C_1 equals 0.001 microfarad; C_2, 0.005 microfarad; C_3, 0.01 microfarad; C_4, 0.1 microfarad.
† No fourth potential.
‡ Other potentials too low to measure.
# Fourth present but too low to measure.

groups. The first group includes somatic motor and sensory fibers of various sizes, the second the myelinated visceral afferents (possibly also somatic fibers), the third myelinated autonomics, both sympathetic and parasympathetic, and the fourth unmyelinated fibers, including those in dorsal roots.

RESULTS

The functional results in three monkeys are presented in the accompanying table. The series of nerves is not large, as the material

was limited, but is adequate to outline fairly well the properties of the four types of nerve fibers characteristic of somatic nerves (figs. 1 and 2) and of the three fiber types characteristic of autonomic nerves (fig. 3). The fastest somatic motor and sensory fibers have a conduction rate on the average of 27 meters per second. The fastest fibers of which measurements were taken had a conduction rate of 38.5 meters per

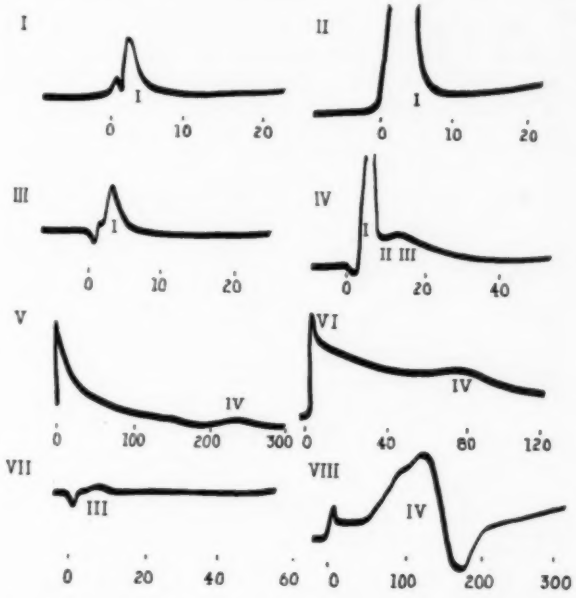


Fig. 1.—*I*, conducted action potential, monkey lumbar motor root; conduction distance 44 mm., temperature 37.5 C. (99.5 F.) and amplification 10 mm. per millivolt. Note the single wave. All time markings in sigma. *II*, same as *I*, with four-panel amplification, 160 mm. per millivolt. Another wave is present, following immediately after the first one. An interval of threshold brings it out. *III*, conducted action potential, monkey lumbar sensory root; conduction distance 55 mm., temperature 37 C. (98.6 F.) and amplification 10 mm. per millivolt. First wave present. *IV*, same as *III*, with 160 mm. per millivolt amplification. Note the two extra waves marked *II* and *III*. *V*, same preparation as *IV*; a stronger stimulus distorts the first part of the record. Note the slower deflection of the base line, and the definite but low fourth wave. *VI*, conducted action potential, monkey vagus nerve; conduction distance 29 mm. and temperature 37 C. The potential due to unmyelinated fibers is seen. The earlier waves are inseparable at the start of this slow line. *VII*, conducted action potential, splenic branch from the celiac plexus; conduction distance 20 mm. and temperature 37.5 C. Note the low first wave. The threshold, conduction rate and rising phase indicate that this potential is derived from myelinated autonomic fibers. *VIII*, same nerve as in *VII*. A large late wave is seen to follow the low first one. This potential has a threshold, conduction rate and rising phase characteristic of unmyelinated fibers. The cross-section of this nerve is shown in figure 4 *VI*. It is seen that only two fiber types are present.

second. The visceral afferent fibers have an average rate of almost 13 meters per second. The average rate of the myelinated visceral efferents is about 5 meters per second, that of the unmyelinated fibers about 0.5 meter. With such a small series it is thought that average rate values are more significant than limiting ones. The thresholds of the potential vary considerably, but in general conform with those obtained for potentials in fibers of corresponding size in the cat (Bishop and Heinbecker [2]). The shortest absolutely refractory period obtained for the somatic fibers is 0.84 sigma, which is roughly a sixth of that pertaining to autonomic fibers. Such a marked difference has been found to hold in all vertebrates so far studied. Attention is directed to the fact that no potential characteristic of unmyelinated fibers has been obtained

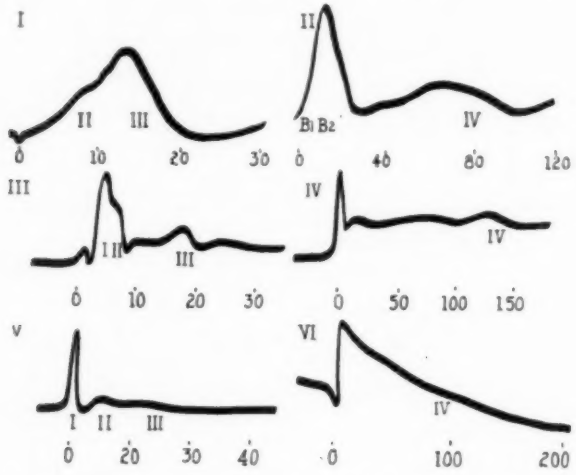


Fig. 2.—*I*, conducted action potential, monkey cervical sympathetic trunk; conduction distance 33 mm., temperature 37 C. The first two potential components are shown. They arise from myelinated visceral afferents and myelinated autonomic efferents, respectively. The visceral afferents are, in general, larger and somewhat more thickly myelinated than the autonomics (fig. 4 *IV*). *II*, same nerve as in *I*, with slower deflection time, to show the myelinated fiber potential. *III*, conducted action potential, monkey femoral nerve; conduction distance 39 mm. and temperature 37.5 C. The first three potential components are present. It is not possible to see the start of the second potential. *IV*, same nerve as in *III*, to show the last wave. *V*, conducted action potential, monkey radial nerve, to show all components except the last; conduction distance 39 mm. and temperature 39 C. (102.2 F.). *VI*, same nerve as *V*, to show the last potential. The deflection time is greater and the stimulus increased.

in any of the motor roots studied (the lumbar region only has been studied). Such a potential is always obtained from sensory roots. Cross-sections of the motor roots studied contain no unmyelinated fibers, whereas cross-sections of sensory roots always do. This bears

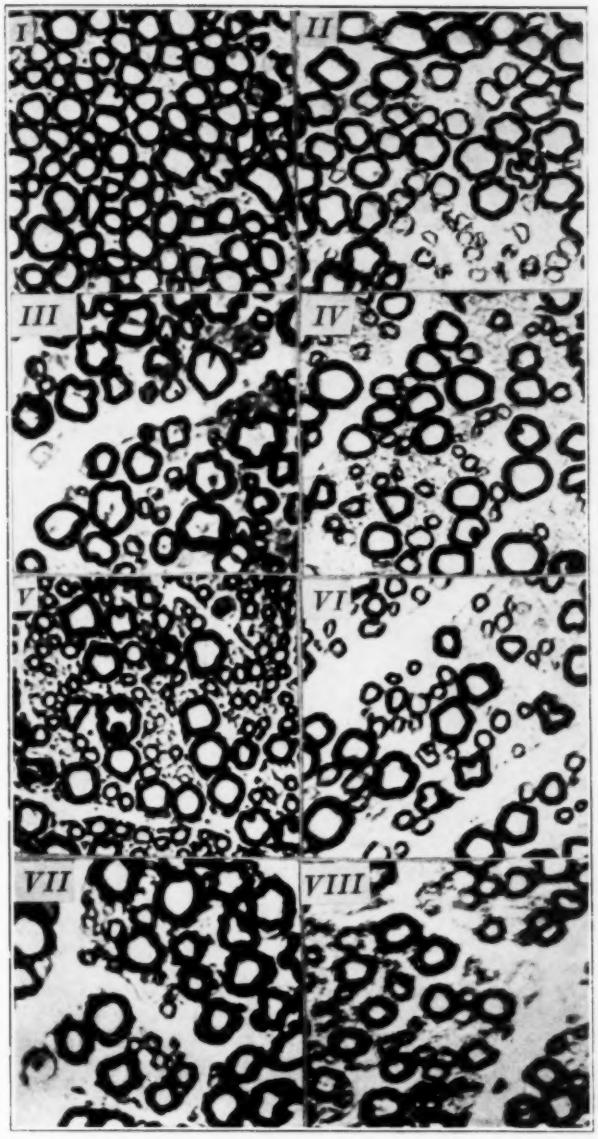


Fig. 3.—*I*, cross-section of hypoglossal nerve. The magnification in this and the other photomicrographs is reduced from 880. The fibers are composed of one type, large thickly myelinated fibers, motor in function. *II*, phrenic nerve in which four fiber types are present. Most numerous are the large, thickly myelinated fibers of motor type. In one area a number of smaller, somewhat more thinly myelinated visceral afferents are mixed with smaller, thinly myelinated autonomics and many unmyelinated fibers. It is usual for these three fiber types to be associated in such groups. *III*, medical cutaneous nerve of the forearm. All four fiber types are present. The large, thickly myelinated fibers in this nerve are presumed sensory in type. *IV*, genitofemoral nerve. This trunk contains many autonomic fibers, especially the small thinly myelinated type. *V*, deep radial nerve. Note the large number of autonomic fibers. *VI*, femoral nerve. Four fiber types are present. *VII*, sciatic nerve. Four fiber types are present. *VIII*, saphenous nerve. Four fiber types are present, but mostly there are large thickly myelinated and smaller, somewhat less thickly myelinated fibers. These are considered to give rise to the first two potential components, respectively.

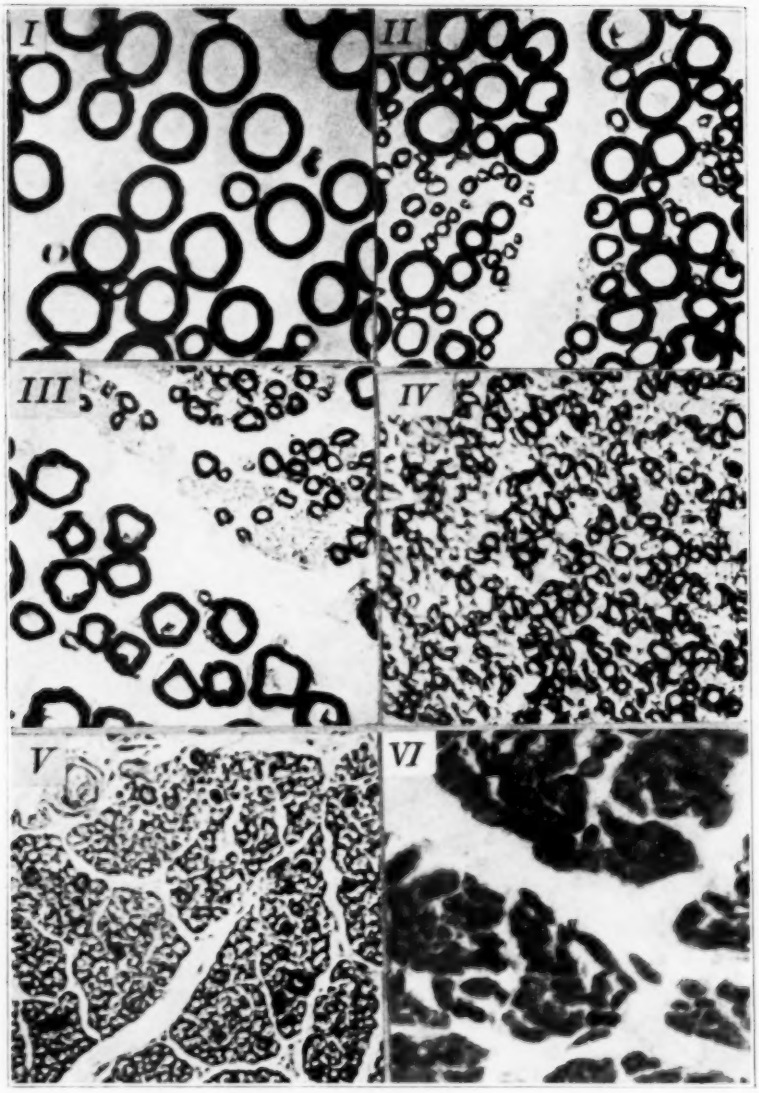


Fig. 4.—*I*, photomicrograph of cross-section of lumbar motor root. The magnification in this and the other photomicrographs is 880. Note the two fiber types. The large fibers are motor. Judgment as to the nature of the smaller myelinated fibers is reserved. *II*, lumbar dorsal root. All four fiber types are present. *III*, cervical vagus nerve. A collection of large thickly myelinated fibers is contributed to the recurrent laryngeal nerve. The autonomic division of the nerve contains three fiber types. The larger myelinated fibers are considered to be visceral afferents. The small thinly myelinated and unmyelinated fibers are autonomic. Judgment is reserved as to the possible existence of unmyelinated afferent fibers in the vagus. *IV*, cervical sympathetic nerve. Three fiber types are present. The number of visceral afferents is not great. *V*, superior cardiac nerve. This nerve is almost completely unmyelinated. There are a few small, thinly myelinated fibers. *VI*, splenic branch of the celiac plexus with unmyelinated and a few scattered, small, myelinated fibers. The action potentials (fig. 1 *VI* and *VIII*) showed a large, late wave and a very small earlier wave, not over 0.5 per cent the area of the others.

out our previous observations that whenever a wave occurs in a nerve potential record propagating at less than a meter per second, unmyelinated axons can be found histologically in the nerve to account for it, and vice versa.

Histologic Analysis.—In figures 3 and 4 are shown the cross-sections of typical somatic and autonomic nerve trunks and lumbar, dorsal and ventral roots. The typical somatic motor and sensory fiber is a larger, thickly myelinated one. The visceral afferents are generally smaller and characteristically less thickly myelinated. The autonomic myelinated fibers are among the smallest and have the thinnest myelin sheaths. The unmyelinated fibers everywhere have properties similar to those of the unmyelinated fibers found in typical sympathetic nerves. There has been no attempt made to differentiate between preganglionic and postganglionic fiber types. Both small thinly myelinated and unmyelinated fibers are found preganglionically and postganglionically. In the turtle's cervical sympathetic (Heinbecker [3]) it has been found that the histologic character of a fiber preganglionically and postganglionically is not different. The question of the validity of Gaskell's hypothesis as regards the histologic character of preganglionic and postganglionic fibers in mammals is being investigated. Results presented to the American Association of Anatomists (1931) indicate that in some mammals (cat) certain myelinated preganglionic axons in the cervical sympathetic synapse with cells having myelinated axons, while others synapse with cells having unmyelinated axons. In the rabbit, however, practically all preganglionic myelinated axons of this nerve synapse with cells having unmyelinated axons. In this respect the monkey resembles the cat rather than the rabbit.

COMMENT

From the standpoint of the functions discussed it has been rather surprising to find that the conduction rates of the somatic fiber types in as active an animal as the monkey are definitely slower than are those of corresponding fibers in the other species studied, even in a species of comparable size and quickness, such as the cat. There is no obvious reason to be offered for this, but it might be suggested that since nerve conduction involves a relatively small part of the time of a reflex response, this function is the least important from the standpoint of physiologic vivacity in general. The fibers are correspondingly smaller in diameter than are those of the cat, which gives at least the same degree of correlation in, if not a biologic reason for, the relation

3. Heinbecker, P.: The Potential Analysis of the Turtle and Cat Sympathetic and Vagus Nerve Trunks, Am. J. Physiol. **93**:384, 1930.

between diameter of fiber and conduction rate. Gasser and Erlanger [4] showed this to hold for certain fibers of various species and even, allowing for differences in temperature, for the corresponding fibers from cold-blooded to warm-blooded animals. This correlation between size and rate even in the slower fibers of the monkey affords us a certain degree of confidence that the nerves employed were in at least as good condition as nerves removed from other animals, and we have no reason to believe that with respect to the functions studied the nerves are not behaving essentially as they would in the normal body, as least until some considerable time has elapsed after removal. One possible exception to this statement should be made with respect to measurements of the absolutely refractory period accompanying excitation. The opinion has been offered previously (Heinbecker [5]) that this measurement gives a better index of the nerve's general condition than does any other measurement available. One of the most cogent reasons for this belief lies in the fact that while this value is accurately measurable it is found to vary considerably, and especially with time after excision and before other measurable functions of the nerve have changed appreciably. When the refractory period is prolonged, other evidences of depression are imminent. Our shortest measurements of this function in the monkey are comparable to those in corresponding fibers in other animals (this value is apparently not correlated with the diameter of the fibers), but generally measurements on the monkey give large values. This may be because, from considerations of economy, as many nerves as possible were worked up from each monkey killed, and nerves that had been out of the body longer than would be otherwise desirable were sometimes utilized. We think that no error will be introduced by assuming the smaller values corresponding to those of other mammals to be correct, and the other functions were presumably not seriously affected by such delay as occurred in their recording.

SUMMARY

Mixed somatic nerves of the monkey (Macacus rhesus) contain four, and autonomic nerves three, fiber types.

These fiber types give rise essentially to four potential components in somatic nerves, and to three in autonomic nerves.

---

4. Gasser, H. S., and Erlanger, J.: The Role Played by the Sizes of the Constituent Fibers of a Nerve Trunk in Determining the Form of Its Action Potential Wave, Am. J. Physiol. **80**:522, 1927.

5. Heinbecker, P.: Effect of Anoxemia, Carbon Dioxide and Lactic Acid on Electrical Phenomena of Myelinated Fibers of the Peripheral Nervous System, Am. J. Physiol. **89**:58, 1929.

The somatic motor and sensory fibers are mostly thickly myelinated. In visceral nerves, in which visceral afferents are presumably isolated, they are usually less thickly myelinated than the larger fibers among axons in somatic nerves, even in proportion to their diameters.

Autonomic efferent fibers are of two types, one small and thinly myelinated and the other unmyelinated.

The histologic and functional analyses of monkey nerves show the fiber types to be similar in distribution to those of the frog, turtle, cat, rabbit and man, except that the somatic fibers are smaller and correspondingly slower in conduction rate.

SPONTANEOUS SUBARACHNOID HEMORRHAGE

ITS RELATION TO ANEURYSMS OF CEREBRAL BLOOD VESSELS

ISRAEL STRAUSS, M.D.
JOSEPH H. GLOBUS, M.D.
AND
SOLOMON W. GINSBURG, M.D.
NEW YORK

The term spontaneous subarachnoid hemorrhage is used in this contribution to designate massive extravasation of blood into the subarachnoid space, caused by spontaneous rupture of a blood vessel. Thus, by definition, the term excludes other forms of bleeding into the subarachnoid space, such as those provoked by trauma causing laceration of brain tissue and blood vessels, those occurring in the course of some systemic disease and those that are but extensions of a massive intracerebral hemorrhage in which disruption of brain tissue allows a direct escape of blood into the subarachnoid space.

Following the classic description by Bramwell [1] of the so-called spontaneous meningeal hemorrhage, numerous contributions have been made on the subject, but they, aside from the comprehensive communication of Symonds [2] and the more recent one by McIver and Wilson,[3] consist mainly of case reports which add little to the early and excellent clinical observations recorded by Bramwell, or else include conditions that are not, in the strict sense, of the type discussed here.

Repeated efforts have been made to establish the cause of subarachnoid bleeding, but no decision as yet has been reached as to what is the basic etiologic factor. It is agreed that a defect in the vessel wall must preexist its rupture and the subsequent hemorrhage. The occurrence of such hemorrhage in young persons, on rare occasions as early as at the age of 10 years, has led many observers to assume that a congenital weakness of the vessel wall, a form of vascular dyscrasia, may be the underlying cause of the final break in the vessel wall. Then

Submitted for publication, June 11, 1931.

From the Neurologic Service and Neuro-Pathological Division of Laboratories of the Mount Sinai Hospital.

Read at the Fifty-Seventh Annual Meeting of the American Neurological Association, Boston, May 27, 1931.

1. Bramwell, B.: Spontaneous Meningeal Hemorrhage, Edinburgh M. J. **32**: 101, 1886.

2. Symonds, C. P.: Spontaneous Subarachnoid Hemorrhage, Quart. J. Med. **18**:93, 1924.

3. McIver, J., and Wilson, G.: Spontaneous Subarachnoid Hemorrhage, J. A. M. A. **93**:89 (July 13) 1929.

again, since in some instances ruptured aneurysms were found in young persons in association with vascular hypoplasia and status thymicolymphaticus, it was further assumed that a defective vessel wall leads first to the aneurysmal deformity, which later under stress and strain ruptures, causing the terminal hemorrhage.

In our experience, arteriosclerosis of cerebral vessels is the most common pathologic condition responsible for the disorganization of the vessel wall, the aneurysmal formation, the rupture and the hemorrhage into the subarachnoid space, irrespective of the age of the patient. Inflammatory lesions of blood vessels due to syphilis or some other infections, such as subacute endocarditis, may also cause similar alterations, but they are less frequent. There are, however, instances in which the degree of the deformity in the blood vessel wall, at the point of the most pronounced degenerative process, is not sufficient to be regarded as an aneurysm. Such defective vessels are frequently overlooked on gross inspection of the brain and are discovered only after a thorough microscopic study. Then again, attention was already called by Reuterwall [4] to the existence of small defects in the form of a small rent in a diseased wall of a vessel, which may often be the cause of hemorrhage.

In a recent contribution on the origin of miliary aneurysms, Forbes [5] called attention to muscular defects in the media of cerebral vessels at the point of their bifurcation. He noted such defects in the pathologic as well as in the normal vessels of the brain and other parts of the body. We can substantiate his observations, but the rather common occurrence of this reduction in width of the muscular coat at a point of bifurcation or branching of a blood vessel leads us to question Forbes' belief that they are congenital anomalies. His observations are, however, significant, for they establish the existence of weak points in a vessel wall, which constitute, as he said, the locus minoris resistentiae, and thus serve as points of predilection for aneurysm formation.

In a recent study and thorough review of the literature on the subject of intracranial aneurysm and its relation to subarachnoid hemorrhage, Schmidt [6] reported that spontaneous subarachnoid hemorrhage, in the great majority of instances, is caused by a ruptured aneurysm. He also stressed the frequent difficulty of finding the aneurysm and emphasized that failure to find an aneurysm does not exclude its existence.

---

4. Reuterwall, O. P.: Ueber bindegewebig geheilte Risse der Elastica interna der Arteria basilaris: Zur Kenntnis der Zerreissungen der Gewebeselemente in der Gefässwand, Stockholm, I. Marcus, 1923; cited by Weber, F. P., and Bode, O. B.: Internat. Clin. **2:1**, 1929.

5. Forbes, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. **47:**239, 1930.

6. Schmidt, M.: Intracranial Aneurysms, Brain **53:**489, 1930.

These views are in full agreement with our own observations, based on the anatomic study of eleven fatal cases and a clinical study of twenty-three cases in which the patient recovered from spontaneous subarachnoid hemorrhage. An analysis of the clinical data collected during the acute and convalescent stages in the recovered cases as compared with the clinical features in the fatal instances lead us to believe that, in the main, the same etiologic factors are operative in the production of the disease picture in the recovered as in the anatomically verified cases.

REPORT OF CASES

CASE 1.—*Previous history of hypertension; precipitate onset of temporary loss of consciousness, severe headache, vomiting and drowsiness, signs of meningeal irritation, neuroretinitis hemorrhagica and blood in the cerebrospinal fluid; rapid decline; death. Necropsy: ruptured aneurysm, subarachnoid hemorrhage.*

History.—R. H., a woman, aged 54, who was admitted to the Mount Sinai Hospital on Dec. 17, 1929, was known to have had hypertension for the preceding twelve years, and on one occasion to have had a severe epistaxis. About five days prior to admission, she was found unconscious on the floor. On regaining consciousness, she complained of severe headache and general weakness. She vomited repeatedly during the next twenty-four hours. Blood pressure readings at that time were 210 systolic and 140 diastolic.

Examination.—The patient's intellect was clouded. There were: rigidity of the neck; blurred disks, with retinal hemorrhages in the right fundus; slight right facial weakness; depressed deep reflexes; absence of right abdominal reflexes, and a right equivocal plantar response.

Course.—The patient continued to be drowsy. During brief periods she was irrational and complained of severe pain in the back of the head and neck. Rigidity of the neck persisted; there were occasional nystagmoid twitchings on lateral fixation of the eyes to the left and diminution of power in all four extremities. All deep reflexes were absent. The blood pressure was 210 systolic and 100 diastolic. The heart was enlarged, and the peripheral vessels were palpable.

A lumbar puncture revealed uniformly bloody cerebrospinal fluid under increased pressure. The Wassermann reaction of the blood was negative. The urine contained a trace of albumin. The temperature on the day of admission varied between 99 and 100 F.; on the second day it rose to 103 F. Signs of congestion developed at the base of the lungs. The patient declined rapidly and died on the fifth day in the hospital.

Necropsy.—Gross Anatomy: When the dura was reflected, a considerable quantity of dark blood escaped. The subarachnoid space contained a large quantity of blood. In the right sylvian fissure, about 2.5 cm. from the circle of Willis, an aneurysm was found in the right middle cerebral artery (fig. 1). The vessel was injected with a dye, and the site of the aneurysmal rupture was determined. The aneurysm measured about 1 cm. in diameter. The larger vessels at the base of the brain showed a moderate degree of atherosclerosis.

Microscopic Anatomy: The subarachnoid space was filled with recently extravasated blood. The pia-arachnoid was moderately thickened. There were some disorganization of the cerebral architecture and mild reactive glial mobilization around the smaller blood vessels.

The basilar artery showed advanced arteriosclerosis with irregular thickening and patchy hypertrophy and degeneration of the intima, splitting of the inner elastic membrane and thinning of the media at irregular intervals. The wall of the middle cerebral artery close to the aneurysm (fig. 2 *A*) showed pronounced degenerative changes in all its coats, such as were described in the basilar artery. The intima was thickened and showed alternately areas of proliferation and degeneration. There were splitting of the elastica and thinning and degeneration of the media (fig. 2 *B*).

Comment.—This case is a good illustration of a ruptured aneurysm with massive subarachnoid extravasation. Unquestionably, the under-

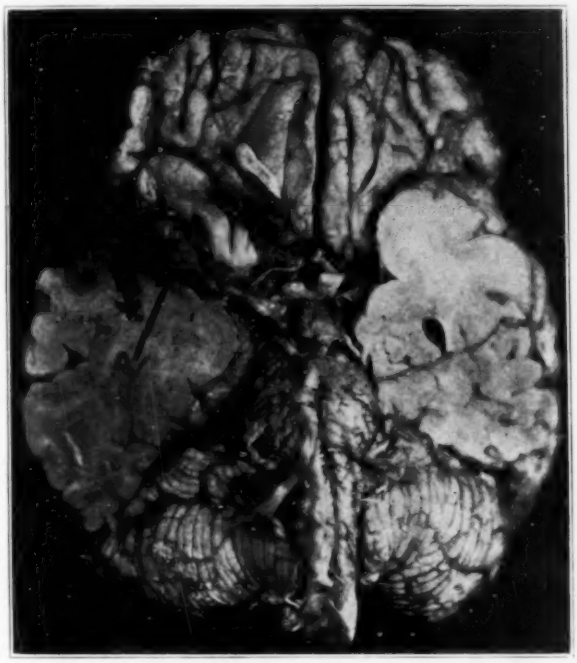


Fig. 1 (case 1).—Base of the brain, showing aneurysm (*A*) of the right middle cerebral artery.

lying cause of the aneurysmal formation is the arteriosclerotic degenerative alteration of the cerebral blood vessels, which is part of the general vascular disease. What brought about the rupture of the aneurysm is not clear from the patient's history, but any stress leading to an increase in blood pressure, as will be seen from a study of other cases, which under normal circumstances is of little consequence, may be sufficient to cause the rupture of a blood vessel if it is diseased and its degeneration is sufficiently advanced.

CASE 2.—*Previously existing hypertension and focal organic disease of the brain; precipitate onset with loss of consciousness, Cheyne-Stokes breathing and*

aggravation of the signs of focal disease of the brain; rapid decline. Necropsy: aneurysm and subarchanoid hemorrhage.

History.—G. L., a woman, aged 61, who was admitted to the Mount Sinai Hospital on Oct. 18, 1929, had been subject to headache for many years. During the preceding two years, the headaches became more frequent and more intense.

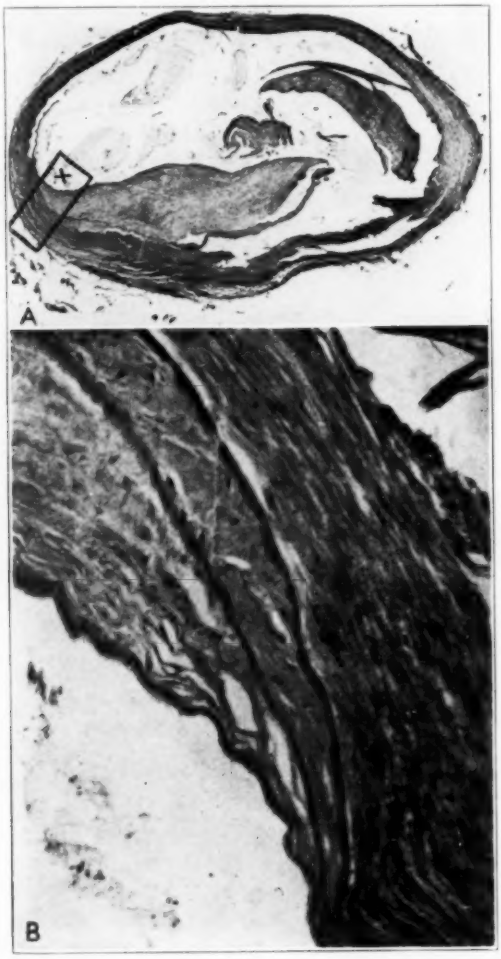


Fig. 2 (case 1).—*A*, cross-section of the middle cerebral artery at a point close to the aneurysmal defect. Weigert's elastic and van Gieson's stains; reduced from a magnification of × 24. *B*, section of the wall of the middle cerebral artery, taken at *X* in *A*. Hematoxylin-eosin stain; reduced from a magnification of × 289.

During the last year she experienced frequent transient episodes of vertigo associated with temporary amnesia and aphasia. These attacks became more frequent and were associated with convulsive seizures. With this there developed dulling

of the intellect. Two days before admission to the hospital, she was seen by a neurologist who elicited pyramidal tract signs on the left and moderate blurring of the left disk. On the following day the patient passed into a convulsive state, became unconscious and was brought to the hospital.

Examination.—The patient was in deep coma. The respiration was of the Cheyne-Stokes type. The blood pressure was 200 systolic and 110 diastolic. There were blurring of the disks and sclerosis of the retinal vessels. The pupils were dilated and reacted sluggishly to light. There was a left facial weakness. The deep reflexes were more active on the left side; the superficial reflexes were diminished. There was a Babinski sign on the left and an equivocal plantar sign on the right.

Course.—A lumbar puncture yielded clear cerebrospinal fluid under increased pressure. The Wassermann reactions of the blood and cerebrospinal fluid were negative. A phlebotomy was performed. There was some temporary improvement, but very soon the patient began to decline. Conjugate deviation of the eyes to the left developed and the head was turned to the same side. She died several hours later.

Necropsy.—Gross Anatomy: When the base of the brain was exposed, blood was noted in the subarachnoid space; it was most marked in the cisterna magna and the interpeduncular cisterna. At the junction of the left middle cerebral artery and posterior communicating artery on the left side, a small aneurysm was found surrounded by a mass of adhesions and a collection of blood. The surface of the brain was smooth and moderately congested. There was a moderate amount of clotted blood in the subdural spaces of the posterior fossa. There was no evidence of fracture of the skull.

Microscopic Anatomy: The pia-arachnoidal space was distended and filled with recently extravasated blood and numerous macrophages. The pia itself showed advanced thickening of old standing. The cerebral cortex showed moderate degenerative changes in the nerve cells and fairly advanced alteration in the architecture. In the white matter there were large accumulations of glial elements (oligodendroglia) about the blood vessels. The latter showed varying degrees of arteriosclerosis.

The basilar artery showed advanced arteriosclerosis; irregular thickening of the intima, with fibrous proliferation and fatty degeneration; there was no definite thickening in the elastic membrane, and only moderate hypertrophy of the muscular coat. The aneurysmal wall, however (fig. 3), showed more advanced arteriosclerotic changes. There was great irregularity in the relative thickness of its constituent layers. The intima in some areas was exceedingly thick, with marked proliferation of fibroblastic elements; in other areas, it showed advanced hyaline degeneration; again in other areas it was entirely absent, leaving an exposed elastic membrane. The latter showed hypertrophy in places, occasional splitting or total loss. The media showed areas of hypertrophy, alternating with areas of hyaline degeneration.

Comment.—A ruptured aneurysm was the cause of the subarachnoid bleeding. Of interest, however, is the fact that a lumbar puncture revealed clear cerebrospinal fluid during life. This may be explained by the early formation of adhesions about the aneurysm, walling off its defective part from the subarachnoid space. These adhesions are very likely the result of local arachnoiditis, caused by the extravasated

blood acting as a foreign body. As a terminal event this protective membrane is broken, and blood, escaping under pressure from a defect in the aneurysm, filled the subarachnoid space and caused the fatal result.

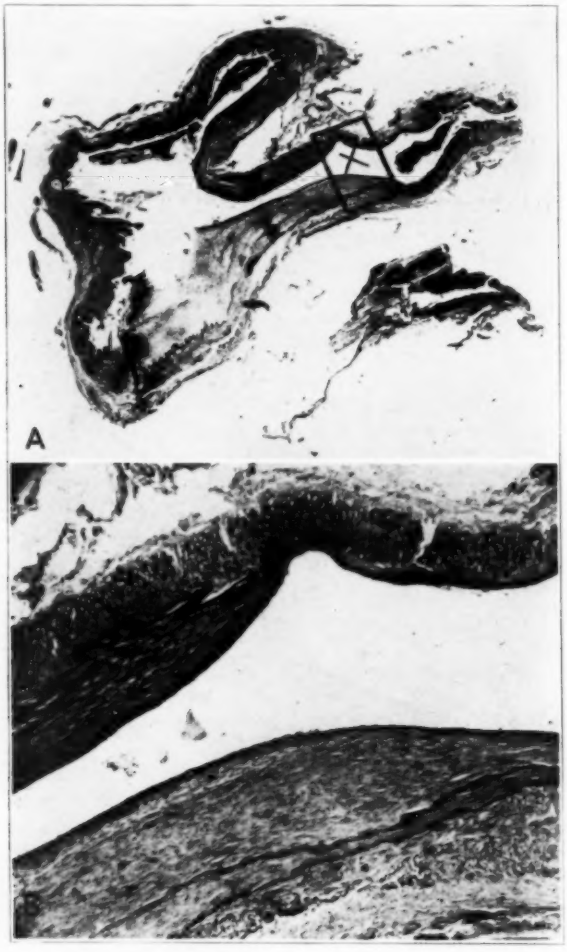


Fig. 3 (case 2).—*A*, cross-section of the aneurysm. Weigert's elastic and van Gieson's stains; reduced from a magnification of × 12. *B*, section of the wall of the aneurysm (field taken at *X* in *A*). Hematoxylin-eosin stain; reduced from a magnification of × 70.

CASE 3.—*A previous attack of disease of the coronary arteries; manifestations of generalized arteriosclerosis and hypertension; sudden onset of stupor; rapid decline. Necropsy: cerebral arteriosclerosis, subarachnoid hemorrhage and syphilitic aortitis.*

History.—A. H., a man, aged 68, who was admitted to the Mount Sinai Hospital on Sept. 19, 1930, one year before had had a sudden attack of precordial pain, inability to breathe and a sense of impending death. He was in bed at that time for two weeks. Since then he had had edema of the ankles and dyspnea on slight exertion. The edema and the shortness of breath had increased steadily.

Examination.—There were irregular, unequal pupils, which were fixed to light but reacted in accommodation; absent deep reflexes; auricular fibrillation; generalized atherosclerosis; a blood pressure of 176 systolic and 52 diastolic; a temperature of 102 F.; a respiratory rate of 22, and a pulse rate of 160. The Wassermann reaction of the blood was negative.

Course.—On the fourth day in the hospital the patient lapsed into deep stupor; Cheyne-Stokes respiration developed, and he died.

Necropsy.—Gross Anatomy: The brain was somewhat large, and showed a marked area of reddish discoloration over the dorsolateral surface of the hemispheres. There were similar areas of discoloration at the base of the brain. All of them appeared to be in the nature of subarachnoid extravasation.

Microscopic Anatomy: Sections of the involved areas showed massive extravasation of blood into the subarachnoid space. The underlying cortex showed no striking alterations, aside from diffuse parenchymatous degeneration in the cortex, moderate gliosis in the white matter and moderate thickening of the smaller blood vessels. The basilar artery showed advanced arteriosclerosis. The intima was greatly thickened in areas, with the proliferative intimal process breaking through the inner elastic membrane and invading the media. In some areas the vessel wall and all its constituent layers had been thinned out to a point where rupture of the vessel could easily occur. A vessel was also found in the region of the more extensive hemorrhage which had the appearance of an aneurysmal expansion and showed well marked arteriosclerosis (fig. 4). No inflammatory changes were noted.

Comment.—A diagnosis of subarachnoid hemorrhage was not made during the life of the patient. It is obvious that it occurred while the patient was under observation. There is little doubt that the defective, fairly large pial vessel ruptured, causing the fatal subarachnoid bleeding, although the point of rupture was not demonstrated. The changes in the cerebral vessels were nonsyphilitic despite the syphilitic lesion in the aorta.

CASE 4.—*Precipitate onset of meningeal signs with blood in the cerebrospinal fluid; apparent recovery; seven months later, bleeding from a lesion in the tongue and recurring meningeal signs; cerebrospinal fluid again bloody; rectal bleeding; rapid decline. Necropsy: generalized arteriosclerosis; old and recent subarachnoid hemorrhages.*

History.—M. L., a man, aged 58, was first admitted to the Mount Sinai Hospital on Nov. 28, 1928, complaining of a stiff neck for seven days, rigidity of the lower extremities for four days and frequent vomiting attacks on the day of admission. Examination revealed rigidity of the neck and a bilateral Kernig sign. A lumbar puncture yielded uniformly bloody cerebrospinal fluid. Repeated lumbar punctures were carried out as a therapeutic measure. The patient reacted favorably and improved rapidly. He left the hospital on Jan. 13, 1929, and remained well for seven months. A lesion then developed on the dorsal surface of the tongue. This was considered to be an epithelioma and radiotherapy was administered. One week

prior to his second admission (September 24), severe headache and rigidity of the neck reappeared. On the day of admission, a profuse hemorrhage occurred from the lesion on the tongue. He became drowsy and was sent to the hospital.

Examination.—The patient was very emaciated; the pupils reacted poorly to light; the neck was rigid; there was a bilateral Kernig sign; the deep reflexes in the lower extremities were not elicited. A lumbar puncture revealed bloody cerebrospinal fluid under increased pressure.

Course.—The meningeal signs remained constant; the disks became blurred. On the tenth day of residence in the hospital, the patient suddenly began to bleed profusely from the rectum and rapidly passed into coma. Proctoscopic examination revealed a bleeding point high up in the sigmoid flexure of the colon. Transfusion was performed. The blood pressure declined rapidly, and two days later the patient died without regaining consciousness.

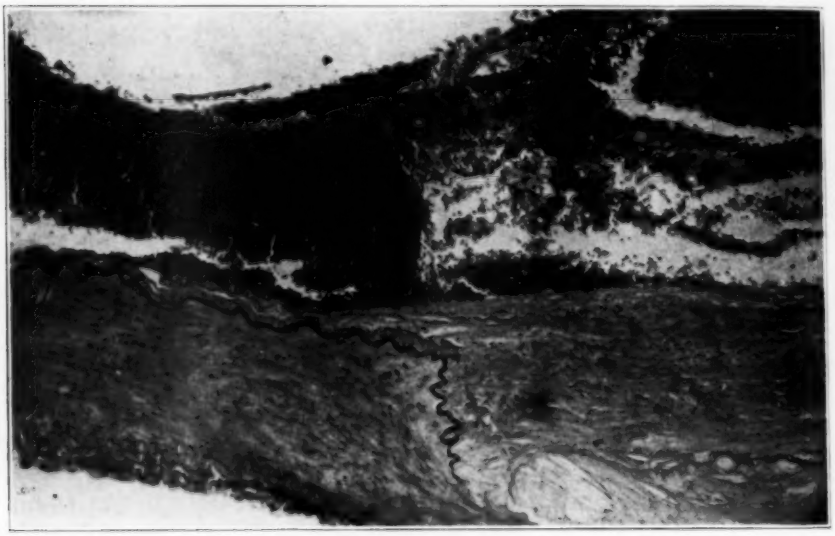


Fig. 4 (case 3).—Arteriosclerosis of a larger pial vessel. Weigert's elastic and van Gieson's stains; × 32.

Laboratory Studies.—On September 25, a blood count revealed: white cells, 24,600; polymorphonuclear leukocytes, 70 per cent; lymphocytes, 30 per cent. The urine was normal. The Wassermann reaction of the cerebrospinal fluid and of the blood was negative.

Necropsy.—Gross Anatomy: The meninges were dull and had an icteric tint, apparently due to old subarachnoid bleeding. This discoloration was plainly seen when the sylvian fissures were opened. There was evidence of recent subarachnoid bleeding over the dorsolateral surfaces of the vermis of the cerebellum and some over the dorsolateral surfaces of both cerebellar lobes. The cerebral vessels revealed marked atherosclerotic changes. There was a moderate degree of hydrocephalus.

Microscopic Anatomy: Histologic study revealed advanced arteriosclerosis of the cerebral blood vessels. The pia-arachnoid was infiltrated with numerous macrophages containing blood pigment, fibroblasts, blood cells and other mononuclear elements. The pial vessels appeared to be thickened and unusually numerous.

Comment.—In this case there were the results of advanced arteriosclerosis. Though no aneurysm was demonstrated, the subarachnoid hemorrhage was unquestionably due to a rupture of a meningeal vessel. The bleeding from the tongue and from the large intestines was likewise due to rupture of similarly diseased vessels. In this instance there was an opportunity to study the meninges three and one-half months after the initial subarachnoid hemorrhage. It disclosed the presence of some disorganized blood and reactive meningeal thickening.

CASE 5.—*Previous cardiovascular disease; sudden onset of cerebral symptoms, with meningeal signs and bloody cerebrospinal fluid; rapid decline; death. Necropsy: encapsulated subarachnoid hemorrhage.*

History.—S. K., a woman, aged 43, who was admitted to the Mount Sinai Hospital on March 19, 1930, had had typhoid fever at the age of 18. She was

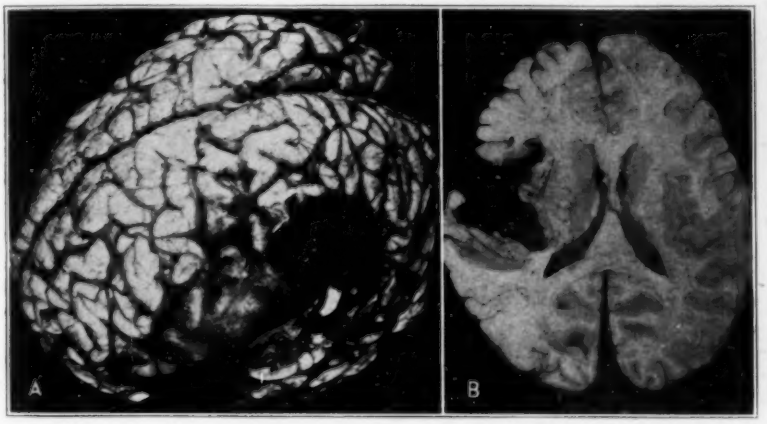


Fig. 5 (case 5).—*A*, encapsulated subarachnoid hemorrhage. *B*, encapsulated subarachnoid hemorrhages as seen on section.

subjected to a curettage for some menstrual disturbance at 34. For some time she complained of increasing dyspnea, palpitation on exertion and edema of the legs. Six days before admission to the hospital, she suddenly became dizzy. She rested for a while and was brought home in a taxicab. She was strong enough to walk up a flight of stairs unaided, but soon complained of severe headache in the occipital region, with intense pain radiating forward. She vomited several times and became alternately drowsy and restless.

Examination.—The patient was somewhat drowsy and complained of headache. There were moderate rigidity of the neck and a bilateral Kernig sign. The pupils were small and unequal; the right was larger than the left. The fundi showed moderate blurring of the disks, more on the right than on the left, with several hemorrhagic areas in the neighborhood of the disk. The retinal vessels were full, the arteries narrow.

Course.—A diagnosis of subarachnoid hemorrhage, probably due to a ruptured intracranial aneurysm, was made and was confirmed by lumbar puncture, which showed uniformly bloody cerebrospinal fluid. The blood pressure was 170 systolic

and 105 diastolic. The hemoglobin was 78 per cent; the white blood cells numbered 18,000; polymorphonuclear leukocytes, 88 per cent; lymphocytes, 1 per cent; monocytes, 1 per cent. The Wassermann reaction of the blood was negative.

The temperature ranged between 100 and 101 F. for about a week. The patient appeared to improve during the first three weeks in the hospital. The blood pressure came down to 120 systolic and 80 diastolic, and then to 100 systolic and 78 diastolic.

On April 8, the patient suddenly collapsed, became pale and did not respond to stimulation. Within a few minutes she passed into deep coma, the breathing becoming shallow and the pulse rate dropping to 60. The corneal and pupillary reflexes disappeared. There were no rigidity of the neck and no Kernig sign. The blood

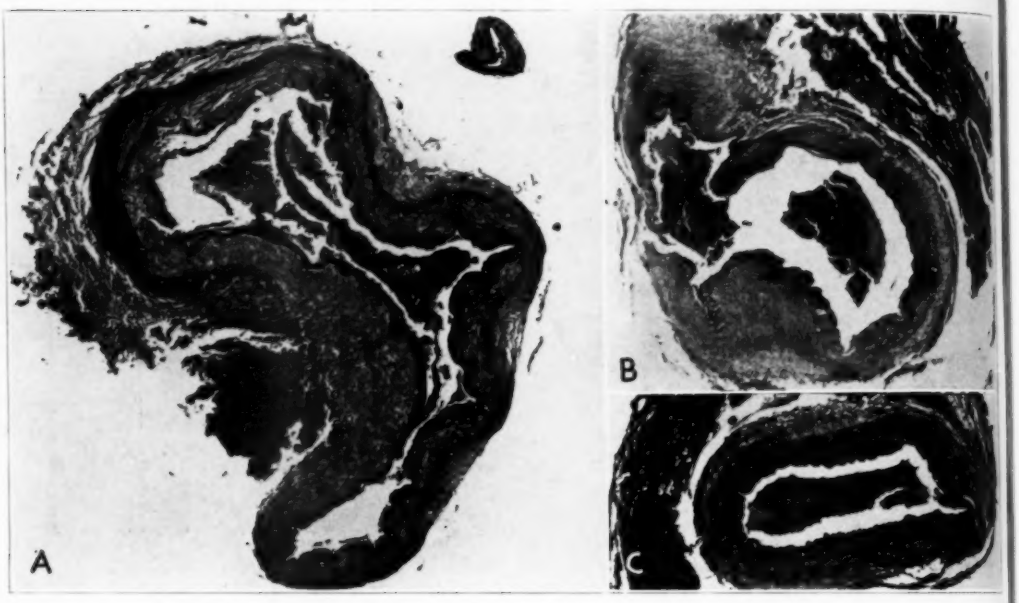


Fig. 6 (case 5).—*A*, basilar artery showing arteriosclerotic changes; × 70. *B*, ruptured blood vessel in the subarachnoid space; × 85. *C*, branching vessel. Weigert's elastic and van Gieson's stains; × 85.

pressure at this time rose to 200 systolic and 120 diastolic. A lumbar puncture yielded clear cerebrospinal fluid under increased pressure. The patient died within a few hours.

Necropsy.—Gross Anatomy: On removal of the calvarium, the dura was found to be distended and showed some discoloration over the left hemisphere. When the dura was reflected, this discoloration was seen to be due to an extensive blood clot over the frontoparietal region. The blood was easily dislodged, and beneath it could be seen an extensive diffuse subarachnoid hemorrhage, which was situated chiefly over the left frontoparietal region (fig. 5 *A*). Running transversely across the upper margin of the sylvian fissure, measuring about 3 cm., was a break in the thickened arachnoid, marking the communication between the subarachnoid and subdural collections of blood. The leptomeninges at the base showed some thickening and yellowish discoloration. There were collections of blood in the cisterna

chiasmatica and interpeduncularis. The fourth ventricle did not contain any blood. There was a large circumscribed subarachnoid hemorrhage in the depth of the left lateral fissure, compressing and occupying the entire insular region and causing marked displacement of the cortex (fig. 5 *B*).

Microscopic Anatomy: There was extensive extravasation of blood into the subarachnoid space. Among the blood elements were numerous macrophages containing pigment material and phagocytosed red corpuscles. The basilar artery showed definite arteriosclerosis(fig. 6 *A*). Vessels in the region of the hemorrhage showed still more advanced degenerative changes. One vessel, with coats undergoing massive degenerative changes, showed at one point a rent in its wall (fig. 6 *B*). It is not unlikely that this defect was responsible, in part at least, for the hemorrhage. Other vessels with irregularities in their walls, as shown in figure 6 *C*, were often seen in this material, as is often the case in apparently normal material. Thinning of the media at a point where a vessel undergoes division or bifurcation has been regarded by some as evidence of malformation (Forbes [5]), but we believe that this is a common occurrence in normal vessels and need not be regarded as an anomaly, although it may serve as a point of predilection for aneurysmal formation.

Comment.—The unusual feature in this case is the limitation of the subarachnoid bleeding. It did not spread widely over the surface of the brain and was apparently confined by adhesions to the area mapped out in the gross description. The existence of fairly definite arteriosclerotic changes in the vessels and coexisting hypertension, despite the age of the patient, points to arteriosclerosis of the cerebral vessels as the cause of bleeding. This case shows how easy it is to overlook a ruptured vessel of this type and how difficult it is to recognize it grossly. This vessel was disclosed only after repeated sectioning of vessels in the vicinity of the hemorrhage.

CASE 6.—*Sudden onset of headache, rise in temperature, focal cerebral signs and meningeal signs; cerebrospinal fluid at first bloody, later clear, with moderate pleocytosis; repeated punctures; cell count increased with each puncture; then fluid again bloody; rapid decline. Necropsy: aneurysm; subarachnoid hemorrhage.*

History.—S. B., a man, aged 40, who was admitted to the Mount Sinai Hospital on March 2, 1929, had been well until eight days before, when he was suddenly seized with a severe headache, at first frontal and then generalized. The headache increased in severity, and was accompanied by a mild rise in temperature and by persistent vomiting.

Examination.—The patient was alert. There was a mild right central facial weakness, and the plantar response on the left was equivocal. The temperature was 102 F., the pulse rate, 72, and the respiratory rate, 20. A lumbar puncture yielded cerebrospinal fluid that at first was bloody; in the process of removal it gradually cleared up. The blood in the first tube was considered as of traumatic origin.

Course.—On the second day, moderate rigidity of the neck and a bilateral Kernig sign were noted. A second lumbar puncture yielded clear cerebrospinal fluid, under moderate pressure, with 90 cells per cubic millimeter, mostly lymphocytes. The blood pressure was 150 systolic and 110 diastolic. A blood count showed 9,700 white cells, with 85 per cent polymorphonuclear leukocytes. The patient's

temperature rose to 103 F., and the pulse rate was 80. He was alternately drowsy and restless. There was constant myoclonic twitchings of the left side of the body.

A diagnosis of meningo-encephalitis was made, and, despite the fact that smears of the cerebrospinal fluid had repeatedly failed to reveal any organisms, intensive treatment with antimeningococcus serum was begun.

The third lumbar puncture, done on the fourth day in the hospital, yielded yellowish fluid with 2,400 cells per cubic millimeter, 90 per cent of which were polymorphonuclear leukocytes. The temperature continued elevated and varied between 103 and 104 F.; the pulse rate was between 90 and 100. Another lumbar puncture on the fourth day again revealed at first yellowish, turbid fluid, but at the end of the procedure the fluid was bloody. The latter was again considered of traumatic origin. The fluid in the first tube showed 4,200 cells per cubic milli-

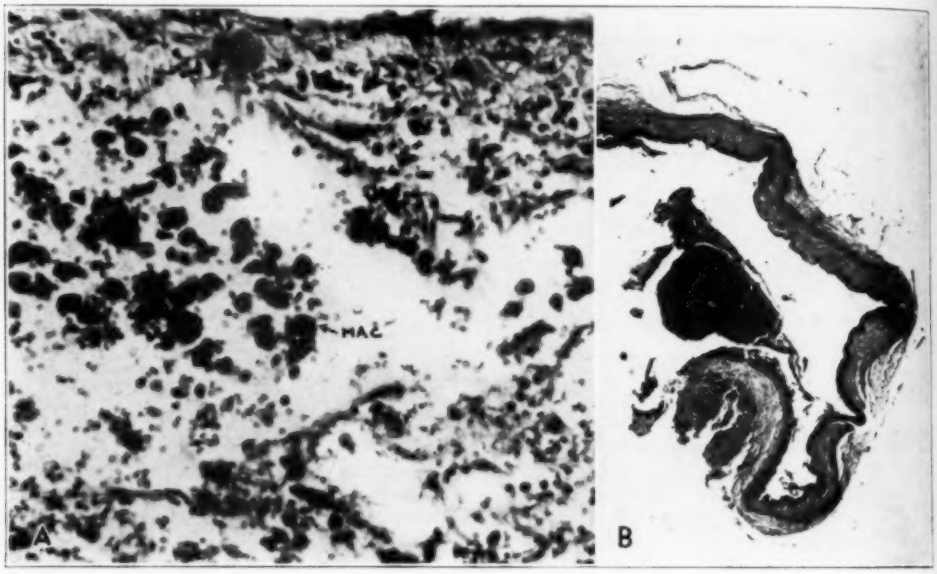


Fig. 7. (case 6).—*A*, pia-arachnoid space filled with disintegrating red blood cells and macrophages (*MAC*). Hematoxylin-eosin stain; reduced from a magnification of × 300. *B*, cross-section of the disintegrating aneurysmal wall. Weigert's elastic and van Gieson's stains; reduced from a magnification of × 26.

meter, 85 per cent of which were polymorphonuclear leukocytes. Two days later, another lumbar puncture yielded frankly bloody fluid. The temperature and pulse rate continued to rise. That afternoon, a combined lumbar and cisternal puncture was done, and bloody fluid was obtained from both needles. Through the lumbar needle the fluid was dark brownish red, while the cisternal needle yielded bright red fluid. The patient grew rapidly worse and died six days after admission.

Necropsy.—Gross Anatomy: The pia-arachnoid was smooth and glistening over the larger portion of the surface of the brain, and showed a moderate amount of discoloration over the parieto-occipital region, due to extravasation of blood into the subarachnoid space. At the base of the brain the arachnoid was smooth and glistening, except for the region of the cisterna pontis, which was filled with recently coagulated blood, and where the meninges showed a moderate degree of

thickening. The vessels were free from decided arteriosclerotic changes and were unusually thin; the basilar artery, however, at 1 cm. posterior to its bifurcation into the posterior cerebral arteries, showed an aneurysm, spherical in outline, which measured about 0.5 cm. in diameter. It was covered by an opaque coating and was embedded in coagulated blood. The fourth ventricle was free from blood. The subarachnoid space around the cord showed layers of coagulated blood at various levels.

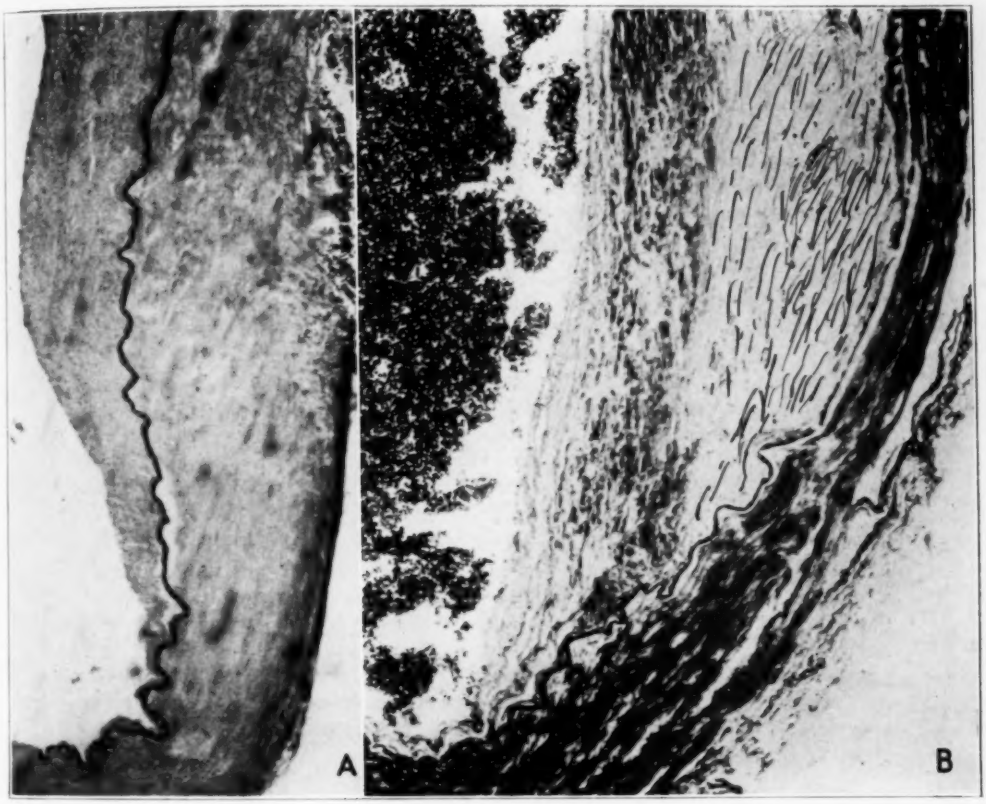


Fig. 8 (case 6).—*A*, wall of the basilar artery. Weigert's elastic stain; × 120. *B*, wall of a vessel close to the aneurysmal defect. Weigert's elastic stain; × 36.

Microscopic Anatomy: There were accumulations of disintegrating cells in the meninges, with numerous macrophages containing pigment and red blood cells, and many fibroblasts (fig. 7 *A*). There were no frank inflammatory changes in the meninges or brain substance. The pial vessels showed decided thickening. The basilar artery and other vessels at the base of the brain, a short distance from the aneurysm, disclosed alterations typical of arteriosclerosis (fig. 8). The aneurysmal wall itself showed a uniform and massive process of disintegration (fig. 7 *B*).

Comment.—In this instance the age of the patient, the lack of a previous history of cardiovascular disease and the high cell count

repeatedly found in the cerebrospinal fluid made it difficult to recognize the true pathologic condition during the clinical course. The discovery of definite arteriosclerotic changes in other vessels adjacent to or remote from the aneurysm and the histologic alterations in the brain and the meninges establish definitely the arteriosclerotic origin of the aneurysm. We offer no explanation for the pleocytosis, which at the beginning led us to consider the case as one of meningitis and induced us to administer antimeningococcus serum. Autopsy showed no inflammatory process in the cranium. In our experience no such pleocytosis occurs as a reaction to bleeding in the subarachnoid space.

CASE 7.—*A previous (seven years before) attack due to cerebral disease, recent recurrence of cerebral symptoms with elevation of temperature; meningeal signs and bloody cerebrospinal fluid; gradual decline; sudden death. Necropsy: aneurysm; subarachnoid hemorrhage.*

History.—A. D., a woman, aged 36, who was admitted to the Mount Sinai Hospital on Dec. 11, 1929, seven years before, while under the stress of a violent emotional outburst, had developed intense pain in the left frontal region, with restlessness and insomnia. Two months later, double vision and pain over the left eye suddenly developed. The pain became more severe. For a while she seemed to have recovered and remained well, except for the diplopia and an occasional attack of pain over the left eye. Two weeks prior to admission to the hospital, pain in the left frontal region suddenly returned. She became stiff "all over" and exceedingly weak. The headache became generalized, and the pain spread down the spine and along the left forearm. The temperature was somewhat elevated, and she experienced an occasional chilly sensation.

Examination.—There was almost complete paralysis of the left third nerve. The left pupil was dilated and fixed to light. There were marked rigidity of the neck, a bilateral Kernig sign, depressed deep reflexes and slight weakness and tremor of the left hand. A lumbar puncture yielded uniformly bloody cerebrospinal fluid, under moderately increased pressure, with xanthochromia on standing. The blood pressure was 142 systolic and 90 diastolic. The Wassermann reactions of the blood and cerebrospinal fluid were negative. The urine contained a slight trace of albumin. A blood count showed: white cells, 11,400; polymorphonuclear leukocytes, 66 per cent; lymphocytes, 21 per cent; monocytes, 12 per cent.

Course.—A diagnosis of spontaneous subarachnoid hemorrhage, due to aneurysm in the interpeduncular space, was made, and repeated lumbar punctures were performed. The latter were mainly to relieve headache when it increased in intensity. In each instance bloody fluid was obtained. The patient did not convalesce satisfactorily, and had several attacks with marked increase in the manifestations of increased cranial tension: slow pulse and signs of meningeal irritation. At one time, when she appeared to be making satisfactory progress, she suddenly passed into stupor, the pulse became unusually slow and a lumbar puncture revealed bloody fluid. She died several hours later.

Necropsy.—Gross Anatomy: The brain was voluminous; the gyri were somewhat flattened. The meninges were dull and showed patchy discoloration, particularly of the left frontoparietal region, where there were accumulations of extravasated blood in the subarachnoid space. There was an icteric hue to the rest of the surface of the brain. The cisterna magna was filled with blood. In an attempt to dissect structures in the interpeduncular space, old adhesions were found, especially

on the left side, making it difficult to separate the left branches of the circle of Willis. This was made more difficult by the exceedingly small caliber of the vessels. The left posterior communicating artery was surrounded by dense granulation tissue and adherent to the adjacent inferior surface of the left temporal lobe. In the course of dissection a small sac broke off from the somewhat thickened posterior artery. This sac, on separation from the adjacent tissue, gave rise to a small aperture through which blood was seen to escape freely. The left temporal lobe over its inferior surface showed marked reduction in consistency and through a small opening, most likely artificially produced, blood escaped on the slightest pressure on that lobe. The ventricles were greatly distended with blood. The left third nerve was displaced laterally and drawn into the granulation tissue. It was soft and brownish red.

Microscopic Anatomy: The histologic changes were similar to those in the previous instances. There were moderate degenerative changes in the brain, recently extravasated blood in the subarachnoid space, thickening and fibrosis of the pia-arachnoid (particularly in the region of the cisterna interpeduncularis), and arteriosclerosis in the larger vessels, particularly of the basilar artery. More advanced changes were present in the aneurysmal wall.

Comment.—Though cerebral aneurysms in young persons are not common, there is clinical evidence in the history of this case to indicate that the aneurysm that caused the fatal hemorrhage probably had existed for seven years. In the adhesions that surrounded the aneurysm, there was very likely the protective scar that had walled off the aneurysm and its defective coats, and thus prevented for seven years the recurrence of a subarachnoid hemorrhage. The aneurysms in younger persons are usually thought to be due to developmental defects. In this case, however, the presence of arteriosclerosis in the cerebral vessels and definite arteriosclerotic changes in the aneurysmal wall indicate that an acquired degenerative process in the cerebral vessels was the most likely cause of the aneurysmal formation, despite the fact that there was no clinical evidence of generalized arteriosclerosis.

CASE 8.—*Sudden onset of headache, followed by convulsions; signs of organic disease of the brain; hypertension, elevation of temperature; glycosuria; bloody cerebrospinal fluid; rapid decline. Necropsy: aneurysm; encephalomalacia; subarachnoid hemorrhage.*

History.—B. C., a man, aged 31, who was admitted to the Mount Sinai Hospital on Oct. 10, 1927, two days before had been suddenly seized with a severe headache. On the following day, three hours before entering the hospital, a convulsive seizure developed and he passed into coma.

Examination.—The patient was in deep coma. The pupils were dilated and fixed. There were rigidity of the neck, bilateral corneal anesthesia, right facial paralysis and spasticity of the right upper extremity. The right abdominal reflexes were absent. There was a suggestion of a Babinski sign on the right. The ocular fundi were normal. The blood pressure was 168 systolic and 95 diastolic. The temperature was 101 F. The urine showed 2.8 per cent of sugar, with acetone 1+ and albumin 1+; the specific gravity was 1.028. A lumbar puncture revealed uniformly bloody fluid.

Course.—A phlebotomy was done on the day of admission, 500 cc. of blood being removed; 40 units of insulin was administered subcutaneously, and 40 Gm. of glucose was given intravenously. The patient died on the same day. The Wassermann reactions of the blood and cerebrospinal fluid were later reported as negative.

Necropsy.—Gross Anatomy: The dura was under marked tension; when it was reflected, a considerable quantity of dark blood escaped under pressure; it contained several clots of varying size. The surface of the brain was covered with blood, and when the base was exposed the subarachnoid space was seen to be filled with blood. The cisternae interpeduncularis and medullocerebellaris were widely distended with blood. The convolutions were somewhat flattened. In the left frontal lobe, on the inferior surface, there was an opening which communicated with an extensive area of softening and cavitation filled with blood clots. Lying free among the blood were a few naked blood vessels. This cavity communicated with the anterior horn of the left lateral ventricle, which was likewise filled with blood. The fourth ventricle, when exposed, also contained blood. The larger vessels at the base of the brain were rather thin-walled. A cavity was present in the region of the left frontal lobe near its mesial surface. The base of this cavity was continuous with a smaller defect in which lay an aneurysm of a small branch of the anterior cerebral artery. Its rupture, breaking through the surface of the brain, filled the subarachnoid space with blood, and invaded the substance of the brain, with consequent leakage into the ventricular system.

Microscopic Anatomy: The wall of the aneurysm showed diffuse degenerative changes in all three coats (fig. 9). In the area of encephalomalacia the brain showed a recent process of softening. In parts other than this area there were no definite alterations in structure.

Comment.—Cases 6 and 7 illustrated the occurrence of an aneurysm in relatively young persons. It is not surprising, therefore, to find a similar condition in this instance. Unfortunately, we were unable to demonstrate the coexistence of arteriosclerotic changes in vessels other than those in which an aneurysm occurred. However, the mild hypertension and the glycosuria, particularly the latter, because of our experience with other verified cases of localized vessel disease in diabetic persons, speak in favor of a local degenerative disease in a cerebral blood vessel. The area of degeneration in the brain must not be looked on as the site of the initial hemorrhage. It is most likely a process secondary to a local vascular alteration that led to the local erosion of the brain tissue. The subarachnoid hemorrhage, as well as the bleeding into the area of softening, were probably provoked by the same cause.

Case 9.—*A previous syphilitic infection; sudden onset of cerebral manifestations; antisyphilitic therapy; temporary recovery; recurrence of cerebral manifestations with signs of subarachnoid hemorrhage; temporary improvement; sudden collapse. Necropsy: meningovascular syphilis, aneurysm and subarachnoid hemorrhage.*

History.—C. G., a colored man, aged 27, who was admitted to the Mount Sinai Hospital on Nov. 13, 1928, had had a chancre five years previously. During the past year he had complained of frequent and severe headaches. Three weeks prior

to admission, he was suddenly seized with a convulsive attack, lasting fifteen minutes, accompanied by loss of consciousness. On regaining consciousness, he complained of double vision. He was confined to bed for two weeks and seemed to improve. He was then seen in the outpatient department of Mount Sinai Hospital, where a positive Wassermann reaction of the blood was reported. He was given a course of antisyphilitic therapy and improved sufficiently to return to work. At the end of one week, however, severe occipital headache reappeared, and he was admitted to the hospital.

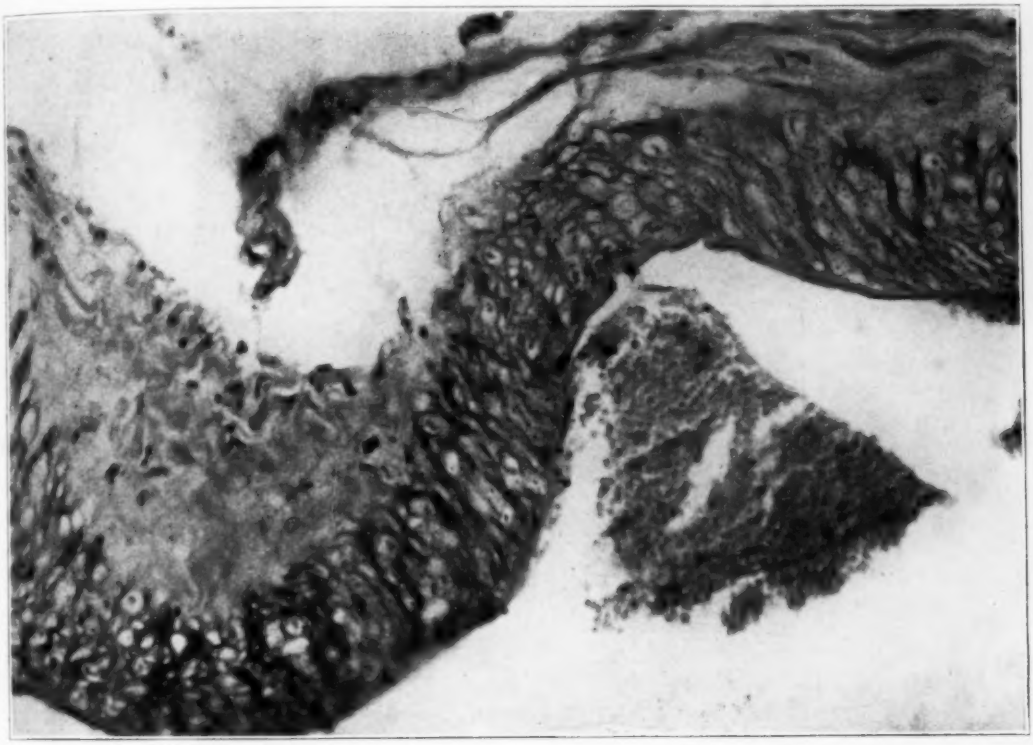


Fig. 9.—Section of the wall of the vessel adjacent to the aneurysm. Hematoxylin-eosin stain; × 290.

Examination.—The patient was drowsy. The pupils were unequal; the left was larger than the right; both were fixed to light. There was limitation of the eye movements in all directions, with skew deviation and ptosis of the left eyelid. The tongue deviated to the right, and there was a right central facial paresis. The deep reflexes and superficial reflexes were depressed. There were marked meningeal signs (rigidity of the neck and a bilateral Kernig sign). The disks were blurred, and a linear hemorrhage was present at the periphery of each disk. A lumbar puncture revealed bloody fluid under increased pressure. The Wassermann reaction of the blood was again reported 4+. The Wassermann reaction of the cerebrospinal fluid was negative. The temperature was 100 F.; the pulse rate was 66, and the respiratory rate, 22.

Course.—Because of the signs of meningeal irritation and the presence of blood in the cerebrospinal fluid, a diagnosis of subarachnoid hemorrhage was made. The neurologic signs, suggestive of a Weber syndrome, pointed to the possibility of a compressing lesion in the interpeduncular space. It was thought that an aneurysm, rupture of which had led to a subarachnoid hemorrhage, was the most likely diag-

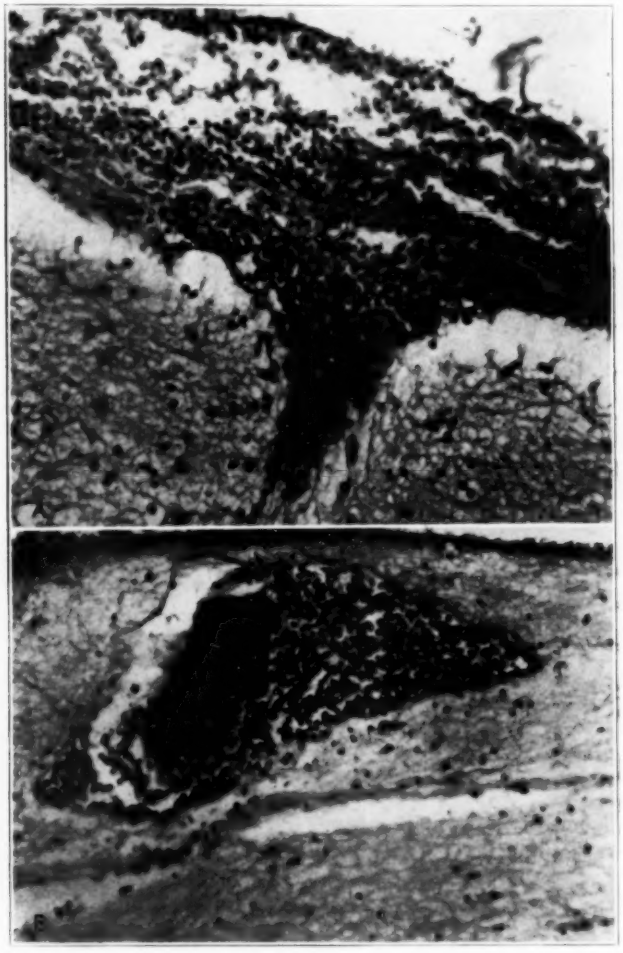


Fig. 10 (case 9).—*A*, meninges, showing lymphocytic infiltration. Hematoxylin-eosin stain; reduced from a magnification of × 220. *B*, perivascular infiltration in the ependymal lining of the ventricles. Hematoxylin-eosin stain; reduced from a magnification of × 280.

nosis. Repeated lumbar punctures and the administration of antisyphilitic therapy led to a gradual improvement. The patient became more alert; the headache became less severe, but the objective symptoms did not change. Seven days after admission, while straining at stool, the patient suddenly complained of severe pain in

the back of the neck. He soon became drowsy, and the pulse rate slowed to 52. He remained in this condition for several days. A lumbar puncture again showed bloody fluid, under increased pressure (530 mm.). The withdrawal of the fluid apparently relieved the headache. The antisyphilitic treatment was again resumed, and the patient began to improve. The meningeal signs abated. The ocular move-

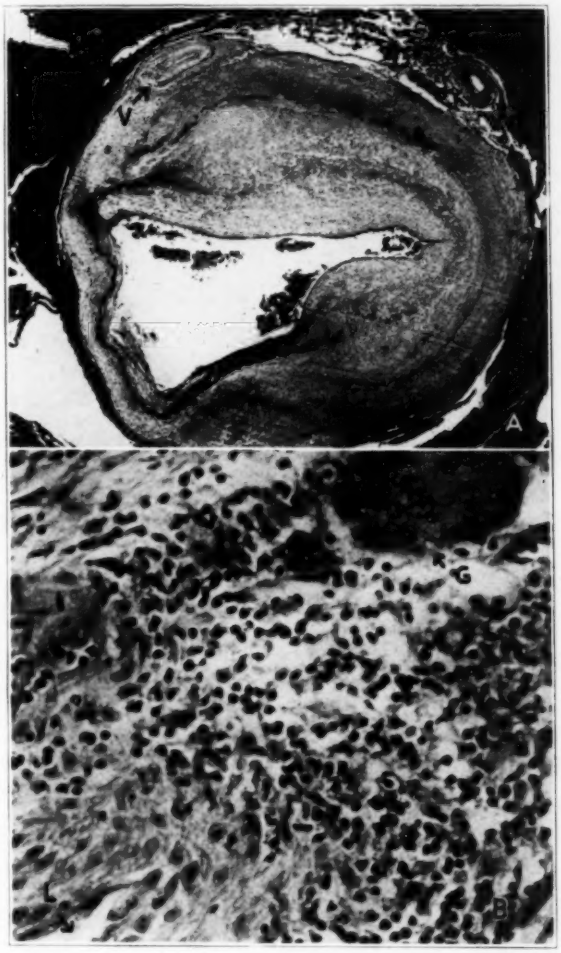


Fig. 11 (case 9).—*A*, basilar artery, showing Heubner's syphilitic endarteritis. Hematoxylin-eosin stain; reduced from a magnification of × 15. *B*, gummatous process in the vasa vasorum in the basilar artery (see *V* in *A*); reduced from a magnification of × 480. *G* indicates a giant cell; *L*, the lumen of the vessel.

ments gained in range, but three weeks later, while receiving an enema, the patient suddenly sank into deep coma and died six hours later.

Necropsy.—Gross Anatomy: There was moderate distention of the ventricles, including the lateral and third ventricles. A small amount of coagulated blood was present in the third ventricle, in the right posterior horn of the lateral ventricle

and in the aqueduct of Sylvius. The latter was also somewhat dilated. The subarachnoid space on the ventral surface of the medulla, pons and midbrain was filled with coagulated blood, in consequence of which the blood vessels could not be seen.

Microscopic Anatomy: The outstanding histologic alterations existed in the meninges, meningeal blood vessels, ependymal lining of the ventricles and the basilar artery. The pia-arachnoidal space was crowded with recently extravasated blood. In such areas there were also many macrophages laden with pigment, and many vessels showing syphilitic alterations. The latter were characterized by lymphocytic infiltrations of the adventitia and intimal thickening of the endarteritis obliterans variety. In areas where hemorrhage was less marked, the pia-arachnoid showed the anatomic alterations of syphilitic meningitis (fig. 10 *A*). The ependyma displayed vessels with similar lymphocytic infiltrations (fig. 10 *B*). Throughout the brain there were perivascular infiltrations, but no parenchymatous changes or glial proliferations. The basilar artery presented features typical of the Huebner endarteritis obliterans, with adventitial changes indicating the presence of periarteritic alterations (fig. 11).

Comment.—This patient suffered from constitutional syphilis. The cerebral vessels showed a picture typical of Heubner's syphilitic endarteritis. There must have been bleeding from the diseased vessel at the time of the convulsive seizures and unconsciousness about six weeks before death. The rent in the vessel must have closed and remained so for weeks, until a renewal of hemorrhage compelled hospitalization. Antisyphilitic treatment and therapeutic lumbar punctures gave relief for a while, but could not restore the integrity of the diseased vessel so as to prevent the fatal rupture.

CASE 10.—*Rheumatic heart disease and episodes of cardiac decompensation; in the course of one attack cerebral symptoms developed: meningeal signs; sudden lapse into stupor. Necropsy: mycotic aneurysm; subarachnoid hemorrhage; encephalitis of subacute endocarditis.*

History.—A. B., a girl, aged 19, who was first admitted to the Mount Sinai Hospital on Dec. 20, 1929, had had rheumatic fever at the age of 5 and an episode of cardiac decompensation at 15. Four weeks before admission, she vomited and had a general feeling of malaise. At the end of three weeks she began to complain of severe frontal headache and pain over the right eye. She had some painful spots in the toes, soles of the feet and one finger.

Examination.—There were signs of cardiovascular disease; a palpable spleen, and petechiae, some of them white centered, some hemorrhagic. The blood pressure was 125 systolic and 50 diastolic. The fundi revealed evidence of neuroretinitis with from 1 to 2 diopters of elevation in each disk. There were some rigidity of the neck and a bilateral Kernig sign. A blood culture revealed Streptococcus viridans. A lumbar puncture yielded clear fluid, under normal pressure, containing 24 cells per cubic millimeter. The Wassermann reaction of the blood and cerebrospinal fluid were negative. A blood count showed: white cells, 35,400; polymorphonuclear leukocytes, 80 per cent; lymphocytes, 17 per cent; monocytes, 3 per cent.

Course.—The headache remained persistently severe and most marked over the right eye. The patient continued to complain of nausea. Flexion of the head was restricted and painful. The temperature varied between 100 and 103 F.; the pulse rate, between 90 and 110, and the respiratory rate, between 20 and 30. On the

fourteenth day in the hospital, the patient suddenly began to vomit, the vomitus contained fresh blood. She passed into stupor; breathing became shallow and irregular; the neck became rigid, and a bilateral Kernig sign reappeared. The eyes moved in a disjointed fashion. All extremities became flaccid, but the deep reflexes were active and a bilateral Babinski sign was obtained. The left side was more paretic than the right. Several hours later, the patient appeared to be somewhat brighter and was able to move the arms. She again vomited a small amount of dark green fluid. She died soon afterward.

Necropsy.—Gross Anatomy: The dura was intact. There was a considerable amount of blood at the base of the brain, most about the region of the brain stem and extending down into the subarachnoid space of the spinal cord. There seemed to be a gap in a portion of the posterior cerebellar artery.

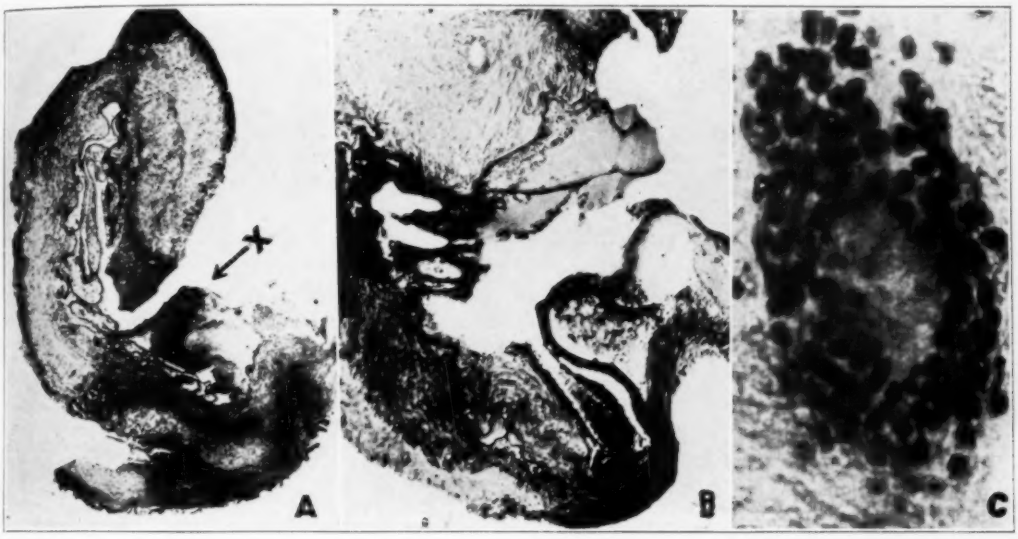


Fig. 12 (case 10).—*A*, ruptured aneurysm. Hematoxylin-eosin stain; × 26. *B*, higher magnification of the field in *A* (marked *X*), showing the displacement of the elastic membrane by blood in the production of a dissecting aneurysm. Hematoxylin-eosin stain; × 40. *C*, perivascular infiltration in the brain stem. Hematoxylin-eosin stain; × 780.

Microscopic Anatomy: A search by serial section revealed a ruptured aneurysmal dilatation of the left middle cerebral artery (fig. 12 *A* and *B*). It showed an advanced inflammatory process, with marked thinning at the point of rupture. In addition, throughout the brain there was a subacute inflammatory process, expressed in perivascular infiltration involving indiscriminately the medium and small blood vessels (fig. 12 *C*), mainly arteries, though the veins were also involved. The subarachnoid space was filled with blood, overshadowing a pre-existing inflammatory reaction. Here and there moderate gliosis was noted.

Comment.—This is the only instance in the group in which a mycotic aneurysm was responsible for the subarachnoid bleeding. Here again, in the early period of the disease lumbar puncture revealed clear fluid,

containing 23 cells per cubic millimeter. However, the presence of swelling of the disks and the meningeal signs suggested the possibility of early oozing with walling off of the hemorrhagic zone, by a reactive meningeal proliferative process, from the rest of the subarachnoid space. The subsequent advance of the meningeal signs and the sudden lapse into stupor may have resulted from a break in this protective wall or from a larger rent in the ruptured aneurysm, with more profuse bleeding into the subarachnoid space. A lumbar puncture at this time would have confirmed the diagnosis. A diagnosis of subacute infective endocarditis was made at the time of admission.

CASE 11.—*Cerebral signs after an unusual exertion becoming more pronounced in a few days; signs indicative of a stem lesion; rapid decline. Necropsy: aneurysm of the basilar artery.*

History.—H. S., a schoolboy, aged 17, who was admitted to the Mount Sinai Hospital on June 6, 1930, had been well until three months before, when his behavior began to show definite disturbances in personality. Two and a half weeks before admission, following the exertion of a long swim, it was noted that the voice was hoarse and that the patient swayed on walking. Four days before admission, he had a ticlike spasm in the left eyelid. He complained of a vague sense of unsteadiness. Two days later, he experienced difficulty in swallowing and delay in urination.

Examination.—The gait was normal. Speech was somewhat dysarthric. There were: bilateral external rectus weakness, horizontal and vertical nystagmus, right facial asymmetry and an absent gag reflex. The palate was paretic, causing regurgitation of food through the nose. There was pseudo-athetosis of the outstretched hand. The knee jerks were more active, and the abdominal reflexes were diminished on the right side; the right cremasteric reflex was absent; there was a bilateral Babinski sign. There was diminution of all forms of sensibility below the third dorsal level, with zones of hyperalgesia at the second and tenth dorsal levels. Lumbar puncture on the day following admission yielded clear fluid containing 40 cells, all monocytes. The Wassermann reactions of the blood and cerebrospinal fluid were negative.

Course.—A diagnosis of encephalomyeloradiculitis was made, and foreign protein therapy was advised. The patient received two intravenous injections of typhoid vaccine, with subsequent chills and a rise in temperature to 102 F. A week later, the cerebrospinal fluid contained 140 cells; 85 per cent monocytes and 15 per cent polymorphonuclear leukocytes. The patient declined rapidly; swallowing became more difficult, and the speech became nasal. The left external rectus weakness became more marked, and ptosis of the left lid appeared. He vomited frequently. Ten days after admission he died with respiratory and cardiac failure.

Necropsy.—Gross Anatomy: The surface of the brain was markedly congested. The convolutions were flattened and the sulci narrowed. Beneath the frontal lobes a round tumor, about the size of a plum and of a dusky blue color, was lying over the ventral surface of the pons; posteriorly, it was found to rise from the junction of the vertebral arteries; anteriorly, the basilar artery was seen to emerge from it (fig. 13*A*). In the pons was a depression caused by the tumor. The tumor was rather soft and compressible. The left trochlear nerve was flattened on the lateral wall of the depression made by the tumor. A moderate bilateral symmetrical hydrocephalus was present.

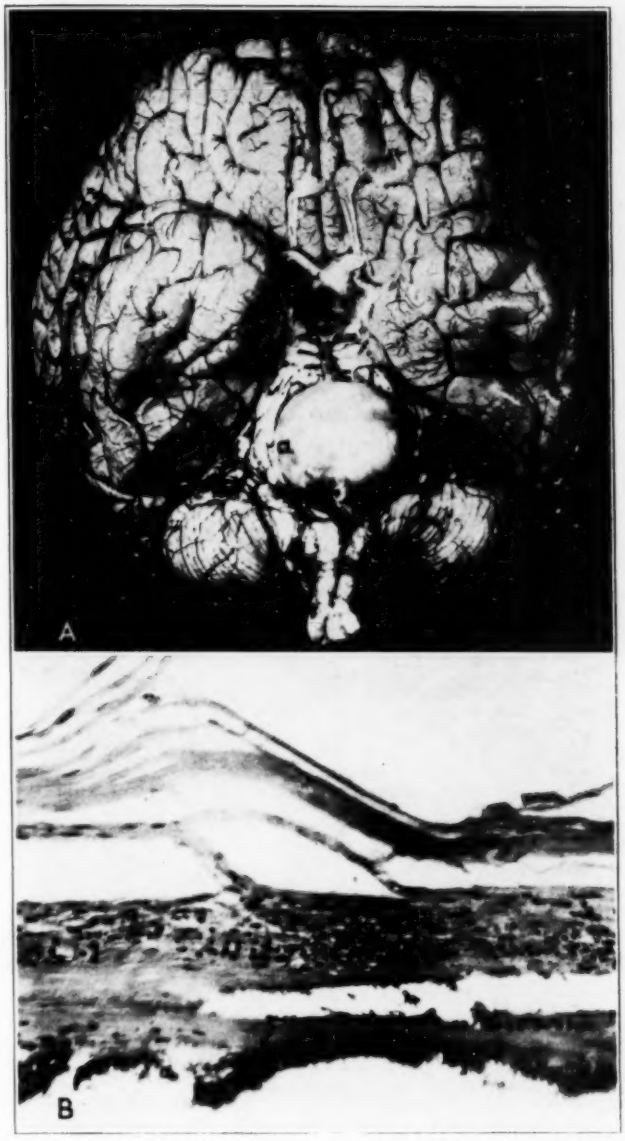


Fig. 13 (case 11).—*A*, base of the brain, showing an aneurysm (*A*) of the basilar artery. *B*, cross-section of the wall of the aneurysm. Hematoxylin-eosin stain; reduced from a magnification of × 70.

Microscopic Anatomy: The wall of the aneurysm, aside from a pronounced general thinning apparently due to unusual stretching, presented alterations that indicated an early arteriosclerosis: marked thickening of the intima and loss of the elastica (fig. 13 *B*). In the muscle coat was an exceedingly large number of nuclei, such as is found in compensatory hypertrophy of the muscle wall. The basilar artery in the proximity of the aneurysm showed moderate and patchy thickening of the intima, such as is found in the early arteriosclerotic alterations of blood vessels (fig. 14).

Comment.—This case is that of the youngest patient in our series of aneurysms. It shows that under certain conditions life may be interrupted before such an aneurysm is ruptured, when the lesion acts as an intracranial tumor. In this case strenuous exertion probably caused

Fig. 14 (case 11).—Intimal thickening in the basilar artery. Weigert's elastic and van Gieson's stains; × 400.

dilatation of a previously diseased vessel, in which there was already the beginning of disease of a degenerative character (probably juvenile arteriosclerosis). There is no evidence of a congenital abnormality in the vessel coats such as has often been mentioned. The pleocytosis in the cerebrospinal fluid and the sensory changes cannot be explained with the aid of the known pathologic changes.

Case 12.—*Recurrent headache for a long time, growing in intensity; sudden onset of convulsive seizures, followed by meningeal signs; bilateral papilledema; xanthochromic cerebrospinal fluid, and signs pointing to a lesion in the posterior fossa; suboccipital craniotomy, but no tumor found; temporary improvement; recurrence of symptoms, with advancing papilledema and more severe headache; ventriculography; rapid decline. Necropsy: aneurysm of the left posterior cerebral artery.*

History.—L. B., a woman, aged 30, who was admitted to the Mount Sinai Hospital for the first time on April 3, 1927, for about two years had had intermittent mild headaches. For the last six months the headaches had become more severe and were localized in the frontal region. One week before admission sudden severe pain in the back and stiffness of the neck developed. She vomited several times. She then had several generalized convulsions, lasting from two to three minutes. On the day preceding admission, there was a slight elevation of temperature.

Examination.—There were rigidity of the neck; a bilateral Kernig sign; bilateral papilledema, and generalized hyporeflexia, the left upper abdominal reflex only being elicited.

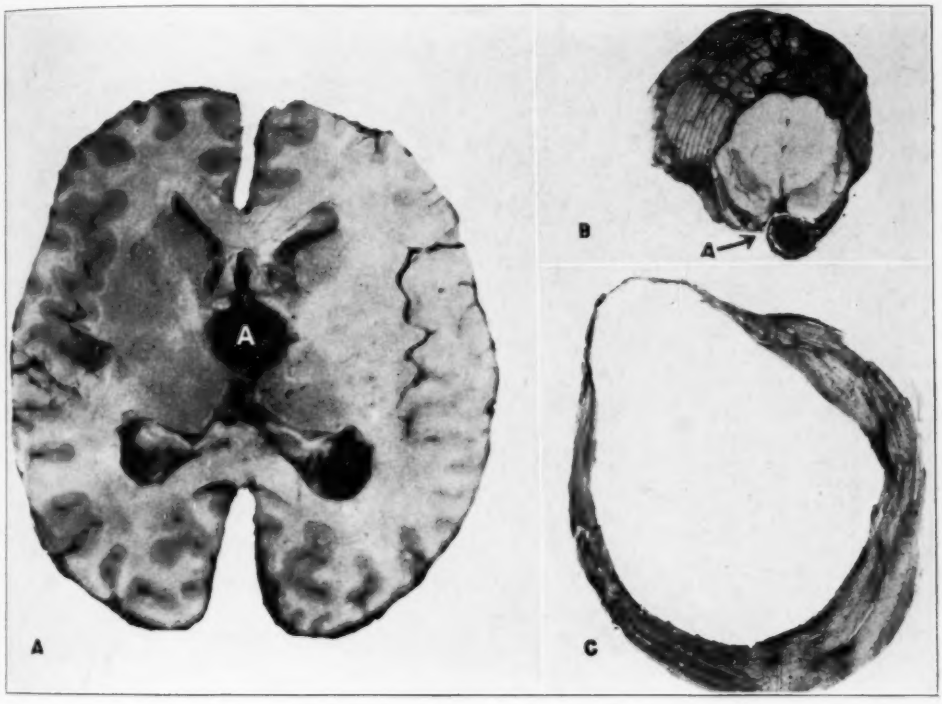


Fig. 15 (case 12).—*A*, horizontal-longitudinal section of the brain, showing an aneurysm (*a*) invading the third ventricle. *B*, cross-section of the midbrain, showing an aneurysm (*a*) under the cerebral peduncle. *C*, cross-section of the disrupting aneurysmal wall. Weigert's elastic and van Gieson's stains; reduced from a magnification of × 40.

Course.—A lumbar puncture yielded xanthochromic fluid; the initial pressure was 340 mm.; there were 33 cells per cubic millimeter, mostly lymphocytes. Lumbar puncture on the following day again yielded xanthochromic fluid. A blood count showed: white cells, 12,800, with 58 per cent polymorphonuclear leukocytes. The Wassermann reaction of the cerebrospinal fluid was negative. On the third day in the hospital, a vertical nystagmus was noted. Six days later, an encephalography was performed. It disclosed moderately dilated lateral ventricles. The third ventricle was poorly filled. In the anteroposterior view, the ventricular

system was apparently displaced to the left, and the right anterior horn seemed to be somewhat larger than the left. A Bárány test showed no involvement of the semicircular apparatus. A diagnosis of neoplasm of the posterior fossa was made. On the sixteenth day after admission, a suboccipital craniotomy was performed. No tumor was found. The patient improved somewhat subjectively and was discharged forty-six days after admission. Throughout the course, the temperature varied between 98 and 102 F., the pulse rate, between 80 and 96. The blood pressure was 110 systolic and 68 diastolic.

Fig. 16 (case 12).—*A*, cross-section of the lower portion of the aneurysmal wall. Weigert's elastic and van Gieson's stains; × 18. *B*, field taken under higher magnification, marked *X* in *A*, showing necrobiosis of the media and hemogenization of the intima; × 40.

Readmission.—The patient was readmitted on June 27, one month after discharge. The headaches were now more severe and constant. Examination at this time revealed right facial weakness; deviation of the tongue to the right; irregular pupils; bilateral papilledema, though not as marked as previously, and an equivocal plantar sign on the right. Twelve days after the second admission, a ventriculography was performed; 60 cc. of clear cerebrospinal fluid was withdrawn and

replaced by air. After this procedure the patient lapsed into stupor. The temperature rose to 103 F., and the pulse rate to 120. A lumbar puncture was done, and xanthochromic fluid was removed. The patient declined rapidly and died twenty-four hours after the operation.

Necropsy.—Gross Anatomy: There was a tumor filling the posterior part of the third ventricle, which measured about 1.5 cm. in diameter and consisted of a rather dense reddish mass encapsulated by a thin, fibrous wall. The ventricles showed a moderate degree of internal hydrocephalus. The tumor arose at the point of origin of the left posterior cerebral artery, and was found to be an aneurysm (fig. 15 *A* and *B*).

Microscopic Anatomy: The pia-arachnoid was moderately thickened and infiltrated with large and small mononuclear elements, gathered mainly about blood vessels. Many of the cells contained pigment material and had acquired the character of macrophages. In the cerebral cortex and subcortex many vessels were surrounded by large numbers of glial elements. The aneurysm contained a well organized thrombus, through which recanalization had taken place. Between the vessel wall and the thrombus, at the periphery of the latter, there was a large collection of monocytes, most of which were macrophages containing pigment, débris and phagocytosed red blood cells. The intima showed a great irregularity in thickness (fig. 16 *A*); at some points it was exceedingly thick, consisting mainly of a reticulum of connective tissue; in other places it was homogenized into a hyalin-like structure; at other points, again, it was totally lost, exposing the elastica. The inner elastic membrane also showed great variability in thickness and alternately splitting, hypertrophy, atrophy or total disappearance. The media displayed advanced necrobiotic changes (fig. 15 *C*), with the muscular coat at points being totally lost and replaced by granulation tissue (fig. 16 *B*). This we believed was due to the closure of the vasa-vasorum incident to the development of the aneurysm with the increased pressure within the lumen and interference with the nutrition of the vessel wall. The alterations in the aneurysmal wall were most likely those of arteriosclerosis.

Comment.—This case is an instance of aneurysm in a young person who presented evidence of intracranial disease for about two years preceding the onset of the final illness. It is not improbable that the aneurysm may be traced as far back and perhaps even beyond that period. Of importance also is the fact that the meningeal signs were associated with xanthochromic cerebrospinal fluid and pleocytosis, indicating that oozing from a break in the aneurysm had occurred at the time when the meningeal signs appeared. It is probable that as the vessel became thrombosed the bleeding stopped and for that reason no free blood was obtained on lumbar puncture. With the thrombosis a new set of signs and symptoms appeared, particularly those of internal hydrocephalus and stem involvement.

Case 13.—*An unusual case of multiple cerebral aneurysms.*

History.—I. S., a woman, aged 59, who was admitted on June 12 and died on June 21, 1924, had had seven children, most of whom had had frequent nosebleeds. The patient had also had frequent nosebleeds. Thirty-two years before, at the age of 27, for a period of two years, the patient had had a few infrequent epileptiform attacks. She then remained free from such attacks until two years before admission to the hospital, when there was a return of seizures; these had since recurred

at the rate of one attack every three or four months. During the past twenty-five years, the patient also had suffered with kidney trouble, which developed in the course of childbirth. At that time she was acutely ill for five or six weeks, passed bloody urine, had swollen feet and had a period of unconsciousness. During the past two months, the epileptiform episodes had become more frequent, occurring from one to four times weekly. The convulsive seizures were described as sudden in onset; the patient would fall to the ground, the body would become rigid and shake, the eyes becoming glassy and the face cyanotic, and froth would appear at the mouth. The attacks would last for about twenty minutes, at the end of which the patient appeared dazed and complained of severe pain in the back of the head. For the last twenty-four hours, the attacks had become still more frequent, occurring almost every half hour. Between the attacks the patient was in a stupor. There was no history of vomiting, chills or rise of temperature.

Examination.—The patient was in coma; no uremic odor was detected. The pupils were unequal, the left dilated and fixed, the right contracted and reacting sluggishly. Convulsive attacks occurred every half hour. They were of jacksonian character; the twitchings, beginning on the left side of the face, would spread to the arm and leg of the same side and then to the right side. The contractions were clonic, and were more marked on the left than on the right side. A lumbar puncture yielded clear fluid, under increased pressure, containing a few red blood cells. The blood pressure was 140 systolic and 77 diastolic. There was apparently no loss of motor power; all deep reflexes were active, more so on the left side; the abdominal reflexes were active; the Babinski sign was present on both sides. The left optic disk had a clear margin and marked pallor; the vessels were thin-walled and not tortuous. The Wassermann reaction of the blood was negative.

The diagnosis made at this time was essential epilepsy and status epilepticus. Large doses of chloral and phenobarbital controlled the epileptiform attacks.

Clinical Course.—During the first few days in the hospital the patient became more alert and cooperative. The convulsions occurred less frequently, but were of longer duration; they were more marked on the left side. Left hemiparesis was now noted, with a left Babinski sign, and fixation of the left pupil. Encephalitis or multiple neoplasms were considered in the diagnosis. The patient's condition soon began to decline. The convulsive seizure had again become more frequent. They were preceded by vertigo and began in the left side of the face, the mouth being drawn to the left; the eyes turned to the left; the left eyelid was closed; the left arm flexed slowly, and simultaneously the left leg began to flex. With this there was no complete loss of consciousness; the patient was able to remember questions that had been asked during an attack. Directly after an attack the left hemiparesis was more marked. The frequency of such attacks, the jacksonian character and the fairly definite localizing signs pointed to a right frontal lesion. Roentgen examination showed marked dilatation of the right anterior diploic veins merging into a calcareous mass in front of the motor area.

On June 20, an exploratory craniotomy was done, and several tumors were found on the surface of the cortex, each globular in appearance and enveloped by a thick capsule; another small mass was felt in the depth of the substance of the brain. The patient died on June 21, twenty-four hours after the operation.

Necropsy.—Gross Anatomy: Aside from some flattening of the gyri in areas other than the diseased portion of the brain and a moderate amount of atheromatous changes in the vessels, no striking changes were noted. The area involved in the disease process was the right frontal lobe, which was definitely smaller than the corresponding portion of the other hemisphere. On the dorsal surface near the dorsal border there was a large vessel running forward, terminating in a small sac

about 1 cm. in diameter. The sac was embedded in a depression about 5 cm. posterior to the frontal pole. When the sac was elevated, a depression was found, lined by smooth glistening pia. Directly posterior to the sac was another elevation, measuring on the free surface about 1.5 cm. in diameter. On cutting into the brain at this point, another larger, encapsulated mass was revealed (fig. 17). This was oval in outline, measured 3 cm. in the long diameter, and was embedded deep in the substance of the frontal lobe. The mass, on section, was hard, somewhat brittle and grayish brown, and gave the impression of an organized thrombus in an aneurysmal cyst. Directly posterior to this, extending back as far as the postcentral gyrus, were several similar cysts, varying from 0.5 to 2 cm. in diameter. The smaller cysts were also well encapsulated, surrounded by thick fibrous, calcified walls. Their cavities were filled with yellowish granular material and a small amount of yellowish fluid; the inner lining of the walls, however, was smooth, grayish white and glistening. All the cysts were easily dislodged from the substance of the brain, leaving behind smooth surfaces of only moderately softened brain substance. All these cystic structures gave the impression of being aneurysmal dilatations of calcified vessels, which appeared to be continuous with that of the cyst.

Microscopic Anatomy: The wall of the sacs had retained some of the histologic features of a medium-sized vessel wall, with its division into adventitia, media and a markedly distorted intima. The last was fused with a highly organized thrombus, which had undergone canalization. The nerve tissue adjacent to the aneurysm showed evidence of softening and mild infiltrative changes with small round cells, apparently a reactive change.

Comment.—This case is a rare instance of multiple aneurysms of old standing. A reevaluation of the clinical history suggests the probability that the epileptic seizures in the early clinical history were synchronous with the formation of the aneurysmal vessel defects. The later disappearance of the epileptiform attacks may then be explained by an adjustment made by the cerebral cortex to this vascular disturbance. As the patient became older, changes unquestionably took place in both the blood vessels and the brain substance supplied by them, and the aneurysms began again to act as irritative foci, with consequent recurrence of epileptic attacks. One can assume that the balance of equilibrium of the brain function was disturbed not merely by the presence of the aneurysms, but also by the degenerative changes associated with advancing years. This case also demonstrates that aneurysms may form early in life and exist for long periods without giving rise to symptoms, and may undergo regressive changes without rupture.

CASE 14.—*Cerebral neoplasm with subarachnoid bleeding.*

History.—A man, aged 41, married, was admitted to the Mount Sinai Hospital for the first time on Aug. 15, 1925, on the third day of an acute illness. Four and a half months previously, he had suddenly fallen and lost consciousness. He had remained in bed for several days and had then apparently recovered. Three days prior to the first admission, while seated, he suddenly vomited. He vomited repeatedly on that day and several times on the following day. There soon developed intense headache, marked rigidity of the neck, generalized weakness, unsteadiness of the hands, a slow speech and a slight rise in temperature (from 100 to 101.5 F.). Examination, at the first admission, revealed marked emaciation,

acute illness and semistupor. The pupils were regular, but unequal, the left larger than the right, and reacted well to light and apparently also in accommodation. The disks showed indistinct margins, and were regarded by the resident staff as showing an early papilledema. There were marked rigidity of the neck with a bilateral Kernig sign; a slight facial weakness, and hyperactive deep reflexes, which

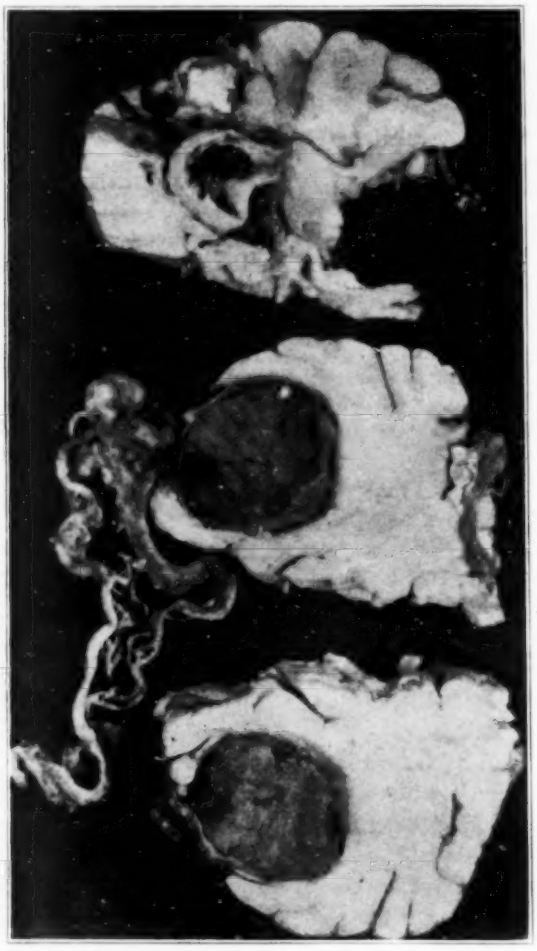


Fig. 17 (case 13).—Multiple, thrombosed and calcifying aneurysms.

were more marked on the right side. The pulse rate was 60. The temperature was somewhat elevated. A lumbar puncture yielded a dark brown, apparently bloody fluid. The blood pressure was 95 systolic and 50 diastolic. A white blood cell count revealed 19,000 cells, with 84 per cent polymorphonuclear leukocytes. The Wassermann reaction of the blood and cerebrospinal fluid was negative.

On the second day of residence in the hospital, the patient suddenly had a convulsive attack. It began with stertorous breathing; the eyes then rolled, with a

tendency toward conjugate deviation to the left; the pupils were dilated and fixed; the arms and legs were extended and fixed in the position of so-called decerebrate rigidity; they relaxed for a short time, to become rigid once more. The deep reflexes were hyperactive, and there was bilateral ankle clonus. The patient came out of the attack, and regained consciousness gradually. On the third day, he was in a better condition. Examination revealed: on sitting up, there was marked tremor of the head (the head was inclined to the right and the chin carried to the left); the right upper extremity showed dysdiadokokinesia, the left some dyssynergia; both lower extremities showed slight ataxia, which was more marked on the right. Neuro-otologic examination showed spontaneous nystagmus to the right in the extreme lateral position, and past pointing inward with the left hand. Stimulation of all canals caused normal nystagmus. The inward past pointing with the left hand was not overcome by the stimulation of the left canals. Stimulation of the right horizontal canal gave an abnormal reaction in the nature of inconstant past pointing. The latter condition and the normal nystagmus pointed, in the opinion of the otologist, to a bilateral intracerebellar lesion.

The diagnosis of the neurologist at this time rested between meningo-encephalitis and intracranial aneurysm.

The patient continued to improve. Another lumbar puncture, on Sept. 23, 1925, yielded clear fluid under slightly increased pressure; there were a few scattered red blood cells and 15 lymphocytes per cubic millimeter.

At the end of two months, the condition improved sufficiently to permit discharge from the hospital, with a diagnosis of aneurysm of a cerebral artery at the base of the brain, with bleeding into the subarachnoid space.

At home, the condition apparently remained unchanged for about six weeks; then, two weeks prior to readmission, the patient began to complain again of intense headache, dizziness and impaired vision. He began to vomit, developed an unsteady gait, falling to the left, and experienced weakness in the left arm and leg. He was readmitted to the hospital on Dec. 31, 1925.

Examination.—There were slight clouding of the intellect, with a superficial emotional reaction; unequal pupils, the left being larger than the right; the latter reacting poorly to light and in accommodation; a few nystagmoid twitchings to the right; bilateral papilledema; left homonymous hemianopia; diminished corneal reflexes; mild central facial weakness; mild left hemiparesis; hyperactivity of the deep reflexes, the left being more lively than the right; less active abdominal reflexes on the left; bilateral equivocal plantar reflex; slight ataxia in all four extremities, with cerebellar hand movements on the left side; unsteady gait, with a tendency to fall to the left and backward (retropulsion); cerebellar tilt of the head to the right, the chin being carried to the left; mild astereognosis, and slight disturbance in the joint sense on the left side. He recognized objects better in the right hand. The cerebrospinal fluid was under slightly increased pressure, but was clear and contained no cells. The hearing was reported by otologists as normal. Caloric tests gave negative results.

Course.—During the first ten days in the hospital the patient presented fairly constant headache, frequent vomiting and gradual decline in mental capacity, but there was no apparent change in the objective signs. In attempting to arrive at a diagnosis, the seat of the lesion was placed on the under surface of the brain supratentorially, in the region of the right temporo-occipital lobe. Such a localization explained most of the focal signs, such as the left homonymous hemianopia, the mild paretic phenomena on the left and some of the cerebellar features, as well as the internal hydrocephalus with manifestations of increased intracranial tension. Manifestations of progressively increasing intracranial pressure and the presence

of signs that localized with fair accuracy the seat of the lesion demanded operative intervention. It was, however, decided to do a ventriculography before operating. While awaiting the operation, the patient suddenly passed through an unusual episode. He first became emotional and restless, waving the right arm and carrying it toward the occiput; the left arm became spastic and flexed, and the left leg became extended and spastic. The eyes were in partial conjugate deviation to the

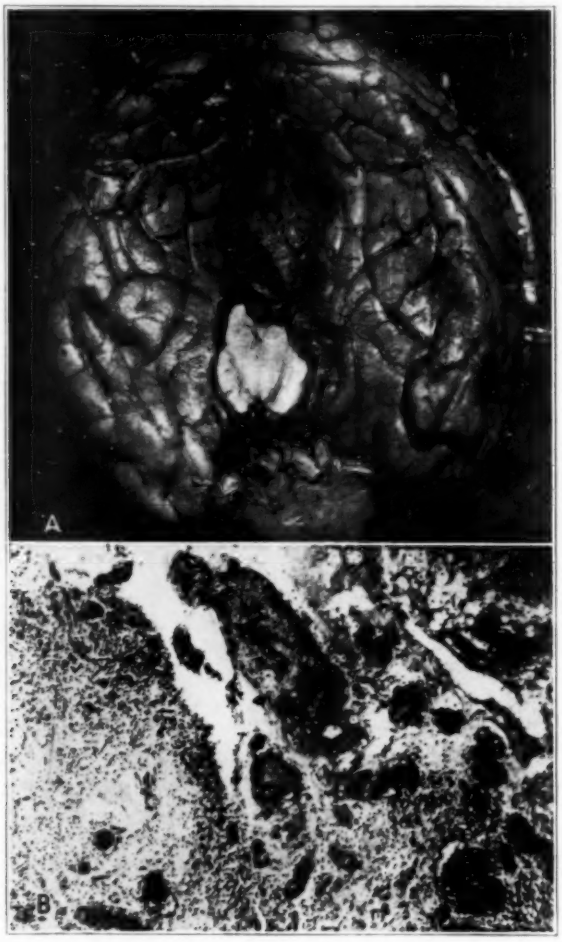


Fig. 18 (case 14).—*A*, base of the brain, showing the appearance and location of the tumor. *B*, photomicrograph of a section of the tumor, showing its marked vascularity; reduced from a magnification of × 40.

right. There appeared bilaterally a Babinski sign and bilateral ankle clonus, which was more marked on the left. This episode lasted for ten minutes and was not associated with complete loss of consciousness, though the patient was somewhat dazed. Following the attack, the Babinski sign and clonus disappeared. On the following day, shortly before the operation, a similar episode of shorter duration took place.

On January 15, a left ventricular puncture was carried out. The fluid was found slightly blood-tinged and under increased pressure. No other unusual observations were made. The patient was returned to the ward in a good condition, but soon afterward there was noted a progressive mental deterioration with progressive elevation of the disks. He died suddenly two days after the ventricular puncture.

Necropsy.—Gross Anatomy: The brain showed evidence of increased intracranial pressure. There was no evidence of meningitis or of free blood on the surface of the brain. The tonsils of the cerebellum were prominent, and gave the impression of having been wedged into the foramen magnum. The pia-arachnoid in this region was somewhat thickened and showed a bluish discoloration. A large tumor was present on the under surface of the right temporo-occipital lobes (fig. 18 *A*), which measured approximately 7 by 4 cm. on cross-section. It was located entirely posterior to the thalamus and lay mesial to the optic radiation. It had broken through to the surface on the mesial side of the right occipital lobe, and dislodged somewhat the mesencephalon to the opposite side, compressing the brain stem in the region of the quadrigeminate plate. The aqueduct of Sylvius was represented by an oblique slit. The tumor was exceedingly friable, dark brown, highly vascular, hemorrhagic and granular; it extended mesially in the region of the forceps major, invading the left occipital lobe in that region. It had broken into the posterior horn of the left lateral ventricle through the mesial wall, which was invaded by tumor tissue. In addition to the main tumor, there were several additional independent centers of growth, located in the anterior part of the left occipital lobe. The ventricles were deflected to the left side, and the posterior part of the left ventricle was collapsed.

Microscopic Anatomy: The tumor was cellular and markedly vascular (fig. 18 *B*), and had all the characteristics of the type previously described under the name "spongioblastoma multiforme."[7]

Comment.—This case, with bleeding into the subarachnoid space, is introduced for several reasons: (1) to show that on rare occasions spontaneous subarachnoid bleeding may occur in conditions other than ruptured aneurysms, as in tumor of the brain; (2) to stress the fact that in our collection of 150 verified tumors of the brain there was only one case in which a tumor gave rise to subarachnoid bleeding during the preoperative clinical course. The clinical picture in the case here described is certainly sufficiently suggestive of a cerebral aneurysm to have warranted such a diagnosis. Errors of this type are likely to recur, but are not serious, since the prognosis in tumors of this type is uniformly poor.

RECORDS OF NONFATAL CASES OF SPONTANEOUS SUBARACHNOID HEMORRHAGE

The clinical features in cases 15 to 36 are presented in the form of a table (see accompanying table); case 37 is described at length in order to give a full account of some of its atypical features and its unusual clinical course.

7. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme: A Primary Malignant Form of Brain Neoplasm: Its Clinical and Anatomic Features, Arch. Neurol. & Psychiat. **14**:139 (Aug.) 1925.

Case, Name, Age, Sex, No.	Past History	Mode of Onset	Examination	Cerebrospinal Fluid	Blood	Urine	Course	Comment
15, J. E., 17 years, male, 200966	Irrelevant	Sudden onset of dizziness while riding on a bicycle; fell and struck head; headache and stiff neck developed soon after	Rigidity of neck; bilateral Kernig sign; blood pressure, 105 systolic and 65 diastolic; temperature, 100 F.; pulse rate, 52; respiratory rate, 18; roentgenogram of skull revealed no fracture	Bloody; Wassermann reaction negative	Wassermann reaction, negative	Normal	The patient improved rapidly. The meningeal signs disappeared. He was discharged two weeks later free from signs and symptoms. For five weeks he remained well, and then he suddenly experienced a sensation as though "something burst" over his left eye. He became dizzy and vomited. He was readmitted to the hospital with rigidity of the neck; a bilateral Kernig sign; unequal pupils, the left larger than the right; paralysis of the left third nerve including ptosis of the left lid; left central facial weakness; diminished abdominal reflexes on the right side; exophthalmos on the left side, and tenderness on pressure over the left eyeball. A lumbar puncture yielded clear fluid under increased pressure, with 8 lymphocytes per cubic millimeter. He improved subjectively, but the objective status remained unchanged. In the course of the next three months he had two other admissions to the hospital, mainly for observation. He was free from symptoms, but the objective neurologic signs remained unchanged.	The diagnostic possibilities considered in this case were intraventricular hemorrhage or pachymeningitis hemorrhagica. In the light of present day knowledge, it may be safely assumed that an aneurysm, as the result of vascular maldevelopment with rupture and oozing of blood into the subarachnoid space, was the most likely cause of the bleeding. The persistent oculomotor palsy places the aneurysm in the interpeduncular space.
16, L. M., 24 years, male, 227850	5 years ago* suddenly developed stiff neck, headache and mild rise in temperature and a transient episode of confusion; two similar attacks in the course of the next 5 years	5 days ago sudden severe frontal headache, vomiting and pain in the back of the neck radiating down the spine; temperature rose to 101 F.	Moderate rigidity of the neck; bilateral Kernig sign; unequal pupils, left greater than the right; bilateral external and internal rectus weakness, left greater than right; slight right facial weakness; generalized hyporeflexia; herpes labialis; systolic murmur at apex; blood pressure, 80 systolic and 50 diastolic; temperature 102 F.; pulse rate 92, respiratory rate, 24	Bloody, under increased pressure; Wassermann reaction, negative; colloidal gold curve, 5555553100	White blood cells, 13,300 polymorphonuclear leukocytes, 60 per cent; lymphocytes, 20 per cent; monocytes, 15 per cent; bleeding time, 1 minute; coagulation time, 8 minutes; Wassermann reaction, negative	Normal	The patient gradually improved. The meningeal and other signs receded slowly. Lumbar puncture 24 days after admission yielded clear fluid under normal pressure with 2 lymphocytes per cubic millimeter. He left the hospital 28 days after admission entirely free from signs and symptoms.	From the history and the symptoms we are fairly certain that this patient suffered from three previous attacks of bleeding into the subarachnoid space, each time making a good recovery. The clinical condition observed by us in the four attacks with recovery indicates the probability of a bleeding aneurysm being the cause of repeated hemorrhages. Of note is the marked similarity between this and the preceding case in the early clinical manifestations and the age of the patients.
17, J. E., 40 years, male, 244694	Irrelevant	5 days ago fainted, fell and struck head; quickly regained consciousness, but	Slight rigidity of neck; questionable Kernig sign; nystagmus in horizontal plane; bilateral external rectus	Blood-tinged, under increased pressure; Wassermann	White blood cells, 14,500; polymorphonuclear leukocytes,	Specific gravity, 1020; albumin, very faint	The patient improved rapidly. Eight days later the cerebrospinal fluid was under increased pressure, with 15 lymphocytes per cubic millimeter. He left the hospital 13 days after	This again was one of the early cases in our series observed at a time when we were not as cognizant of the syn-
		dizziness and som-	weakness; slight right central facial weak-	reaction, negative;	85 per cent; lymphocytes, 14 per cent;	trace	admission free from signs and symptoms.	drome of subarachnoid hemorrhage as we are now, and a diagnosis of pachymeningitis hemor-

J. E., 40 years, male, 244694		fell and struck head; quickly regained consciousness, but	questionable Kernig sign; nystagmus in horizontal plane; bilateral external rectus	under increased pressure; Wassermann	cells, 14,500; polymorphonuclear leukocytes,	gravity, 1020; albumin, very faint	days later the cerebrospinal fluid was under increased pressure, with 15 lymphocytes per cubic millimeter. He left the hospital 13 days after	The early cases in our series observed at a time when we were not as cognizant of the syn-
		dizziness and somnolence persisted	weakness; slight right central facial weakness; tongue deviated to right; upper deep reflexes increased; knee jerks and ankle jerks diminished; upper abdominal reflexes greater than lower; plantar responses equivocal; blood pressure, 110 systolic and 50 diastolic; temperature, 100.6 F.; pulse rate, 76; respiratory rate, 20	reaction, negative;	85 per cent; lymphocytes, 14 per cent; monocytes, 1 per cent; Wassermann reaction, negative	trace	admission free from signs and symptoms.	drome of subarachnoid hemorrhage as we are now, and a diagnosis of pachymeningitis hemorrhagica interna was made. Our later experience with this type of case leads us to believe that our first diagnosis was incorrect.
18, M. K., 32 years male, 248486	Influenza 6 years ago; pneumonia 3 years ago	9 days ago, while lifting heavy weight, experienced sudden severe headache and nausea; the day following there was a recurrence of nausea and headache, also difficulty in urination	Marked rigidity of neck; bilateral Kernig sign; slight narrowing of palpebral fissures, right greater than left; nystagmus in all directions; right central facial weakness; upper deep reflexes diminished; knee jerks and ankle jerks absent; abdominal reflexes active; systolic murmur at apex transmitted into axilla; blood pressure, 118 systolic and 60 diastolic; temperature, 102.4 F.; pulse rate, 80; respiratory rate, 24	Xanthochromic under normal pressure, with 185 lymphocytes per cubic millimeter; Wassermann reaction, negative;	White blood cells, 11,000; polymorphonuclear leukocytes, 72 per cent; lymphocytes, 26 per cent; monocytes, 1 per cent; hemoglobin, 100 per cent; Wassermann reaction, negative	Specific gravity, 1,020; albumin, trace	On discharge from the hospital 12 days after admission, the only positive neurologic findings were unequal pupils, the left larger than the right, and an absent right ankle jerk.	The xanthochromic fluid is evidence of a hemorrhage having occurred a number of days previous to admission. The character of the spinal fluid and the rapid recovery indicate that the bleeding was mild. The presence of a large number of lymphocytes is a frequent late reaction in cases of intracranial hemorrhage during the period of recovery.
19, G. S., 48 years female, 248608	Irrelevant	8 days ago sudden onset of severe frontal headache; next day pain in back of head, rigidity of neck, nausea and vomiting; one day ago several chills and rise in temperature	Patient acutely ill; marked rigidity of neck; bilateral Kernig sign; pupils dilated (right reacted more promptly); hyperemia and blurring of margins of right disk; bilateral external rectus weakness; ptosis of left eyelid; facial asymmetry; deviation of tongue to right; upper deep reflexes diminished; knee jerks and ankle jerks absent; inequality of abdominal reflexes; right greater than left; weakness of both lower extremities; blood pressure, 140 systolic and 80 diastolic; temperature, 100.5 F.; pulse rate, 60; respiratory rate, 18	Bloody, under increased pressure (cell count unreliable); Wassermann reaction, negative;	Wassermann reaction, negative; white blood cells, 8,200; polymorphonuclear leukocytes, 64 per cent; lymphocytes, 32 per cent; monocytes, 4 per cent;		The patient improved rapidly. Lumbar puncture 12 days later yielded clear fluid under normal pressure, with 9 lymphocytes per cubic millimeter. On discharge, 20 days after admission, there were slight bilateral external rectus weakness and generalized hyporeflexia. The patient was seen two months later, when she was free from signs and symptoms. Six months later she collapsed in the street and died.	The recurrence with fatal issue indicates the probability that in this instance an aneurysm existed. A partial defect caused the first attack, while a larger tear caused massive extravasation and a fatal issue.

Clinical Features in Cases 15 to 36—Continued

Case, Name, Age, Sex, No.	Past History	Mode of Onset	Examination	Cerebrospinal Fluid	Blood	Urine	Course	Comment
20, S. T., 39 years, male, 255591	3 months ago fell from roof and sustained a fractured ankle	6 days ago, following coitus, experienced sudden pain in occipital region; generalized headache continued for two days; on the third day was free from symptoms, but on the fourth day, on attempting to sit up, he felt pain about the waist and in the legs; this was followed by rigidity, which spread rapidly from the lower extremities to the neck; the temperature rose	Rigidity of neck; bilateral Kernig sign; right pupil greater than left; left knee jerk greater than right; blood pressure, 148 systolic and 100 diastolic; temperature, 101 F.; pulse rate, 96; respiratory rate, 20	Bloody; pressure, 190 mm.†; Wassermann reaction, negative;	White blood cells, 10,200; polymorphonuclear leukocytes, 84 per cent; lymphocytes, 16 per cent; Wassermann reaction, negative		The temperature dropped to normal the day following admission. The cerebrospinal fluid, 3 days later, was still bloody. Five days later it was xanthochromic. There was a rapid recovery. The patient remained in the hospital 32 days. Seventeen months later she was reexamined and was found to be free from signs and symptoms.	
21, A. S., 48 years, male, 259902	Irrelevant	4 days ago suddenly developed a severe persistent headache; two days later complained of diplopi	Marked rigidity of neck; bilateral Kernig sign; margins of both disks blurred; sclerotic changes in retinal vessels; pupils unequal, left greater than right; both irregular; bilateral external rectus weakness; right central facial weakness; generalized hyperreflexia, right greater than left; plantar responses equivocal; blood pressure, 110 systolic and 70 diastolic; temperature, 99 F.; pulse rate, 68; respiratory rate, 20	Blood-tinged, under increased pressure, with 33 cells per cubic millimeter; 80 per cent lymphocytes (cell count unreliable); Wassermann reaction, negative;	White blood cells, 14,500; polymorphonuclear leukocytes, 75 per cent; lymphocytes, 18 per cent; monocytes, 4 per cent;	Normal	On the second day in the hospital, lumbar puncture revealed xanthochromic fluid under increased pressure, with 24 lymphocytes per cubic millimeter. The fundi showed pericapillary edema with a few hemorrhages. A third puncture 8 days later, yielded clear fluid, under increased pressure, with 5 lymphocytes per cubic millimeter. The right disk was edematous. Improvement set in; the papilledema receded. The patient left the hospital with residuals of papilledema and a slight right central facial weakness. He was in the hospital 37 days. He was seen in the follow-up clinic; there was no change in the status. He complained of periodic headache.	This is the first case in this series in which hemorrhagic neuroretinitis, rather characteristic of subarachnoid hemorrhage, was noted.
22, S. B., 57 years, male, 261103	Pulmonary tuberculosis at age of 28; influenza at 50; pneumonia at 56	7 days ago sudden onset of severe headache, rise in temperature and vomiting; complained of intense pain radiating from top of head	Rigidity of neck; bilateral Kernig sign; pupils unequal, left greater than right; bilateral ptosis; bilateral external rectus weakness; slight right central facial weak-	Xanthochromic, under normal pressure, with 5 cells per cubic millimeter, all	White blood cells, 15,000; polymorphonuclear leukocytes, 88 per cent; lymphocytes, 12 per cent;	Normal	The second puncture on the ninth day revealed clear fluid under normal pressure, with 45 lymphocytes per cubic millimeter. The meningeal signs gradually disappeared. A third lumbar puncture revealed clear fluid under normal pressure. The temperature varied from 99 to 101 F.	

		to neck and arms, stiffness of neck and photophobia	ness; generalized hyperreflexia; blood pressure, 140 systolic and 75 diastolic; temperature, 99 F.; pulse rate, 100; respiratory rate, 20	lymphocytes; Wassermann reaction, negative;	Wassermann reaction, negative		The patient left the hospital at the end of 31 days, free from signs and symptoms.	
23, M. Q., 50 years, female, 263418	Trauma to the left eye 40 years ago; headache for last six months following a fall; struck on head by awning 2 months ago, with no apparent sequelae	Sudden transient loss of consciousness on day of admission followed by mental confusion, severe headache, restlessness, irritability and repeated vomiting	Slight mental confusion and marked restlessness; rigidity of neck; right pupil widely dilated and fixed to light; left contracted and sluggish; (old trauma) arteriosclerotic changes and blurring of margins of disk in left eye; ocular movements in lateral planes restricted; generalized hyporeflexia; abdominal reflexes absent; right equivocal plantar responses and left Babinski sign; blood pressure, 120 systolic and 90 diastolic; temperature, 99 F.; pulse rate, 100; respiratory rate, 22	Bloody, under increased pressure; Wassermann reaction, negative;	White blood cells, 15,200; polymorphonuclear leukocytes, 78 per cent; lymphocytes, 16 per cent; monocytes, 6 per cent; Wassermann reaction, negative; coagulation time, 23 minutes; bleeding time, 4½ minutes; Torniquet test, negative	Specific gravity, 1,022; albumin, faint trace; many hyaline and granular casts	During the second week in the hospital the temperature rose to 101 F.; the pulse rate was 20; the respiratory rate, 32. Ptosis of the left eyelid, a purpuric eruption and herpes labialis developed. The cerebrospinal fluid, on repeated punctures, was bloody, later becoming xanthochromic. The patient gradually improved; she left the hospital 22 days later, free from meningeal signs. The other findings remained unaltered.	On May 5, 1931, 5 years and 1 month after her discharge from the hospital, the patient was reexamined. For the last two months she had been bedridden. The neurologic status revealed a complete motor aphasia, unequal pupils, the right larger than the left, which did not react to light or in accommodation; right hemiparesis; generalized hyporeflexia; the right great toe was maintained in the Babinski position; coarse tremor of the right hand, and masklike facies. It is most likely that an aneurysm in the course of the left middle cerebral artery in the neighborhood of the foot of the left precentral gyrus was responsible for the local cerebral signs, and that a rent in this aneurysm caused the subarachnoid bleeding.
24, D. C., 50 years, female, 273194	For many years headache, becoming more frequent during last 10 years	4 days ago found unconscious; could not be aroused; appeared rigid; regained consciousness 3 hours later; next day became alternately drowsy and restless; left side paralyzed; had urinary retention	Semistuporous; poorly oriented; speech slow and thick; moderate stiffness of neck; bilateral Kernig sign; blurring of disks, with neuroretinitis hemorrhagica; bilateral external rectus paresis; horizontal nystagmus; slight vertical nystagmus; left hemiparesis; generalized hyporeflexia; absent abdominal reflexes; equivocal plantar response on left; blood pressure, 130 systolic and 90 diastolic; temperature, 100.4 F.; pulse rate, 98; respiratory rate, 34	Bloody, under increased pressure; Wassermann reaction, negative;	Wassermann reaction, negative	Specific gravity, 1,020; albumin, traces; few casts	The patient made a rapid recovery. Lumbar puncture 15 days after admission yielded xanthochromic fluid containing 20 lymphocytes per cubic millimeter. On discharge from the hospital, 30 days after admission, the neurologic status was negative except for retinal pigmentation.	In this case we met for the first time in this series manifestations of a focal lesion in the motor area. Because of the complete recovery it is not likely that a hemorrhage occurred first in the cerebral cortex and was followed by secondary extravasation into the subarachnoid space. We are more inclined to the belief that a break in the wall of an aneurysm adjacent to the cerebral cortex led to the subarachnoid bleeding.

Clinical Features in Cases 15 to 36—Continued

Case, Name, Age, Sex, No.	Past History	Mode of Onset	Examination	Cerebrospinal Fluid	Blood	Urine	Course	Comment
25, L. B., 25 years, female, 287755	Irrelevant	6 weeks ago abrupt onset of intense headache with rise in temperature and occasional vomiting; headache persisted; one week ago there appeared rigidity of neck and more frequent vomiting	Restless, noisy, irrational; marked rigidity of neck and retraction of head; bilateral Kernig sign; bilateral papilledema with retinal hemorrhage; bilateral external rectus weakness, right greater than left; impaired conjugate movements of eyes to right; right central facial weakness; generalized hyporeflexia; equivocal plantar response on right; blood pressure, 135 systolic and 90 diastolic; temperature, 100 F.; pulse rate, 62; respiratory rate, 34	Bloody, under normal pressure; Wassermann reaction, negative;	White blood cells, 14,000; polymorphonuclear leukocytes, 84 per cent; lymphocytes, 16 per cent; Wassermann reaction, negative		There was a stormy clinical course with fluctuations in the clinical picture. There were an initial advance in the papilledema and a periodic increase in the intensity of the meningeal signs. At the end of 3 weeks improvement set in. The cerebrospinal fluid became clear. The swelling of the disks receded, but atrophic changes appeared. On discharge 3 weeks after her admission, there were slight papilledema with beginning atrophic changes in the disks; slight bilateral external rectus weakness and right central facial paresis. Nine months later neurologic examination gave negative results.	This case is striking because of the complete recovery despite the long period of active bleeding, the stormy course and the protracted convalescence.
26, B. G., 54 years, male, 291947	"Grip" in 1927; buzzing in left ear for last 3 weeks	Eleven days ago sudden pain in lumbar region radiating to neck, frontal headache and vomiting; 5 days ago more severe pain and headache with difficulty in urination; rise in temperature on day of admission	Marked rigidity of neck; bilateral Kernig sign; slight haziness of disks, right greater than left; pupils sluggish to light; generalized hyporeflexia; left Hoffmann sign; blood pressure, 120 systolic and 64 diastolic; temperature, 100.6 F.; pulse rate, 56; respiratory rate, 18	Bloody, under normal pressure; Wassermann reaction, negative;	Wassermann reaction, negative	Specific gravity, 1,020; albumin, trace	Repeated spinal punctures revealed bloody fluid until the eleventh day. It then became xanthochromic, and finally, on the thirteenth day, clear. There was rapid symptomatic improvement. The patient left the hospital after 23 days, free from signs and symptoms. Nine months later he was apparently well.	The unusual feature here is the localization of pain in the lumbar region. On May 2, 1931, two years and 10 months after his discharge from the hospital, the patient was examined. He complained of a heavy feeling in the head, buzzing in the left ear and general weakness. The neurologic status disclosed no objective signs.
27, J. M., 22 years, male, 299594	Irrelevant	Headache for two weeks; 3 days ago, after taking several drinks, vomited repeatedly; rigidity of neck, pain behind eyes and transient impairment of hearing developed	Slight rigidity of neck; mild Kernig sign on right; old chorioretinitis; deep reflexes unequal, left greater than right; Babinski sign on right; equivocal plantar response on left; sensory changes of radicular type in arms and legs; temperature, 100.5 F.; pulse rate, 65; respiratory rate, 14	Bloody; pressure, 180 mm.	White blood cells, 13,000; polymorphonuclear leukocytes, 75 per cent; Wassermann reaction, negative; bleeding and clotting times, normal	Normal	Repeated punctures yielded bloody fluid. There was improvement after the twelfth day. On the twenty-fourth day, headache reappeared. Lumbar puncture revealed fresh bleeding. Meningeal signs and vomiting reappeared for a brief period during the next nine days. Uninterrupted improvement followed. The patient was in the hospital 2 months and 4 days. One year later, he was free from signs and symptoms, with no residuals aside from slight hyperreflexia and the retinal pigmentation.	The presence of an old chorioretinitis indicates that some preexisting systemic disease might possibly have some bearing on the development of an aneurysm in a young person. Of interest here also is the cerebrospinal fluid pressure, which was unusually high, without signs of papilledema, and the recurrence of bleeding while the patient was under observation, after a brief period of apparent recovery.
28, E. G., 25 years,	During past four years four consec-	Two weeks ago complained of pain in right lower	Marked rigidity of neck; bilateral Kernig sign; bilateral papil-	Blood-tinged, Wassermann reaction,	White blood cells, 6,500; polymor-	Specific gravity, 1,020;	The cerebrospinal fluid was repeatedly bloody until the fifth day after	The four eclamptic pregnancies very likely re-

28, E. Q., 25 years, female, 306178	During past four years four consecutive pregnancies were accompanied by eclamptic manifestations; pulmonary tuberculosis disclosed four years ago, not substantiated by roentgen examination of chest; frequent headaches for four years; loss of weight, anorexia and lassitude for past 8 weeks	Two weeks ago complained of pain in right lower quadrant; there was elevation of temperature for two days; five days ago she was awakened by sudden headache and pain in back of neck; she vomited and lost consciousness for several hours; temperature again rose for one day	Marked rigidity of neck; bilateral Kernig sign; bilateral papilledema with hemorrhages, right greater than left; bilateral external rectus paralysis; unequal knee and ankle jerks, left greater than right; right abdominal reflexes not elicited; systolic murmur over precordium, not transmitted; blood pressure 186 systolic and 130 diastolic; temperature, 100 F.; pulse rate, 72; respiratory rate, 30	Blood-tinged, Wassermann reaction, negative;	White blood cells, 6,500; polymorphonuclear leukocytes, 84 per cent; lymphocytes, 14 per cent; monocytes, 2 per cent; Wassermann reaction, anticomplementary	Specific gravity, 1,020; albumin, very faint trace; occasional granular casts and red blood cells	The cerebrospinal fluid was repeatedly bloody until the fifth day after admission, when it became brownish and turbid, with 40 polymorphonuclear leukocytes per cubic millimeter. The meningeal signs and loss of deep reflexes were still noted on the fifth day. On the eighth day, clear cerebrospinal fluid was obtained, with 200 cells per cubic millimeter, mostly lymphocytes. The blood pressure dropped to 135 systolic and 85 diastolic. There was a rapid regression of signs after the fifth day in hospital. There were no cells in the cerebrospinal fluid on the eleventh day. The patient was in the hospital 17 days. Three days after discharge she suddenly collapsed and died.	The four eclamptic pregnancies very likely resulted in damage not only to the kidneys, but also to the vascular system, including the vessels of the brain, producing an aneurysm, the rupture of which caused the hemorrhage.
29, M. G., 17 years, male, 306269	Pneumonia at age of 3 years; scarlet fever at 7 years	While on a ladder struck head (?) and fell to floor; soon afterward severe headache, stiffness of neck, rise in temperature and chilly sensations developed; became confused, vomited repeatedly, became irritable and was amnesic for events preceding admission to hospital	Marked rigidity of neck; bilateral Kernig sign; nystagmoid jerks in horizontal plane; generalized hyperreflexia; bilateral Babinski sign; blood pressure, 110 systolic and 70 diastolic; temperature, 100 F.; pulse rate, 72	Bloody; Xanthochromic on centrifugation	White blood cells, 7,200; polymorphonuclear leukocytes, 84 per cent; lymphocytes, 8 per cent; monocytes, 8 per cent; Wassermann reaction, negative	Normal	The patient was given four injections of antimeningococcus serum; two intrathecally and one each intravenously and intramuscularly. The fluid remained blood-tinged until the eighth day in the hospital; then xanthochromic until the fifteenth day, when clear fluid was obtained. There was symptomatic improvement; the signs disappeared on the twenty-third day. The patient was in the hospital 45 days. There were no objective signs and no complaints when he was seen one year later.	The patient was reexamined on May 5, 1931, 1 year and 7 months after his discharge from the hospital. He had no complaints, and the neurologic status disclosed no objective findings.
30, M. A., 54 years, female, 307700	Irrelevant	Took to bed with pain in shoulders and frontal headache diagnosed as "grip"; 10 days later on attempting to rise from bed, fell to floor, vomited and became incontinent of feces; headache continued for three weeks; vision became impaired for last two weeks, and right eyelid ptosed for two days; generalized convulsion on day of admission	Moderate rigidity of neck; bilateral Kernig sign; fundi showed advanced arteriosclerosis with hemorrhages; total palsy of right third nerve; left external rectus weakness; right central facial weakness; blood pressure, 162 systolic and 88 diastolic; temperature, 100 F.; pulse rate, 78; respiratory rate, 20	Bloody; Wassermann reaction, negative;	White blood cells, 16,000; polymorphonuclear leukocytes, 56 per cent; lymphocytes, 44 per cent; urea nitrogen, 9 mg.; Wassermann reaction, negative		The headache gradually disappeared, but fresh retinal hemorrhages appeared; these were, however, soon absorbed. The palsy of the right third nerve and weakness of the left sixth nerve persisted. The patient was in the hospital 115 days. She left the hospital free from subjective symptoms. The last report on her chart, 11 days before discharge, said "no change in status."	The persistence of the palsy of the third nerve indicates the existence of an aneurysm in the interpeduncular space, the rupture of which, it may be assumed, caused the subarachnoid bleeding. On May 11, 1931, 17 months after discharge, the patient was reexamined. She had no complaints other than attacks of precordial pain. The neurologic status revealed; residuals of the palsy of the third nerve on the right (paralysis of the right superior and inferior rectus muscles); the right pupil fixed to light and in accommodation and larger than the left; the left pupil sluggish to light; arteriosclerosis of the retinal vessels.

Clinical Features in Cases 15 to 36—Continued

Case, Name, Age, Sex, No.	Past History	Mode of Onset	Examination	Cerebrospinal Fluid	Blood	Urine	Course	Comment
31, Y. A., 48 years, female, 308673	Irrelevant	4 days ago, while dancing, fainted; recovered consciousness in a few minutes; soon afterward developed severe pain in back of neck; vomited repeatedly, passed into semistupor, and remained in this condition for four days	Marked rigidity of neck; Kernig sign on left; bilateral external rectus weakness; generalized hyporeflexia; absent abdominal reflexes; bilateral equivocal plantar response; blood pressure, 150 systolic and 100 diastolic; temperature, 101.5 F.; pulse rate, from 40 to 46; respiratory rate, 20	Bloody; Wassermann reaction, negative;	White blood cells, 10,000; polymorphonuclear leukocytes, 75 per cent; sugar, 83 mg.; urea nitrogen, 17 mg.; Wassermann reaction, negative	Albumin, trace; hyaline casts	On the sixth day incomplete paralysis of the right third nerve developed. Headache increased in severity. On the following day, the right sixth and seventh nerves became paretic. The blood pressure dropped to 90 systolic and 50 diastolic, and on the tenth day (in the hospital) gradual improvement set in. The patient was discharged 39 days later free from signs and symptoms. One month later she again collapsed and was taken to another hospital.	
32, P. A., 25 years, male, 310526	Gonorrhea twice; chancre 2½ years ago; received 9 injections of arsphenamine and several of mercury	3 weeks ago had mild infection of upper respiratory tract, with several nosebleeds; two weeks ago mild headache which gradually became more severe; swelling of glands of the neck for one week; three days ago lapsed into semistupor; was taken to another hospital, where lumbar puncture failed to relieve headache; character of fluid at that time not known	Moderate rigidity of neck; bilateral Kernig sign; right pupil irregular; deep reflexes diminished; left knee jerk greater than right; right ankle jerk greater than left; upper abdominal reflexes absent; acute pharyngitis; palpable inguinal and epitrochlear glands; blood pressure, 110 systolic and 80 diastolic; temperature, 99 F.; pulse rate, 80; respiratory rate, 18	Blood-tinged; supernatant fluid; xanthochromic; Wassermann reaction, negative;	White blood cells, 5,000; polymorphonuclear leukocytes, 39 per cent; lymphocytes, 53 per cent; eosinophils, 3 per cent; monocytes, 5 per cent; Wassermann reaction, negative	Normal	The Meningeal signs disappeared after 15 days in the hospital. The patient complained of pain in the left lumbar region and tenderness over the left sacroiliac joint. He was in the hospital 23 days. When seen 5 months later, he had unequal reflexes in the lower extremities; the left knee jerk was more active than the right; the right ankle jerk was more lively than the left, and there was a herpetic eruption over the eighth dorsal vertebra, with pain in this zone.	The history of a chancre, despite the negative Wassermann reaction, may be regarded as strong evidence of vascular syphilis with aneurysm formation in a cerebral vessel. In our series there is only one other case of syphilitic vascular disease (see case 9).
33, M. G., 43 years, male, 316466	Irrelevant	5 days ago suddenly became dizzy, fainted and fell to the ground; lost consciousness for one minute; headache and nausea since then	Slight rigidity of neck; slight right central facial weakness; right knee jerk and ankle jerk greater than left; right Babinski sign; blood pressure, 110 systolic and 80 diastolic; temperature, 99 F.; pulse rate, 76; respiratory rate, 20	Xanthochromic, under increased pressure; 2 cells per cubic millimeter; Wassermann reaction, negative;	Wassermann reaction, negative	Normal	There was a rapid symptomatic improvement. The patient left the hospital 13 days after admission, with a right central facial weakness and the right knee jerk more active than the left.	The patient was reexamined on May 3, 1931, 9 months after his discharge from the hospital. He had no complaints. The neurologic status disclosed no positive findings, aside from a slight right central facial weakness.
34, M. S., 35 years, male, 316526	Irrelevant	Five days ago, after lifting weight, patient suddenly became dizzy and vomited; he be-	Moderate rigidity of neck; bilateral Kernig sign; right pupil greater than left; right central facial	Xanthochromic; 7 cells per cubic millimeter; Was-	Wassermann reaction, negative	Occasional red blood cell and cast	The patient improved rapidly. A second lumbar puncture, 10 days later, yielded clear fluid. On discharge from the hospital 17 days later, there were inequality of the	Mild exertions under normal conditions do not usually precipitate such serious events. In this instance, the bleeding

pupils, the right larger than the left, and right central facial weakness.

into the subarachnoid space from a ruptured

male, 316526		became drowsy and complained of pain in back of head and behind eyes; 4 days ago had stinging pain in epigastrium; headache increased in severity	weakness; signs of old fibrosis at right apex; blood pressure, 110 systolic and 70 diastolic; temperature, 100.6 F.; pulse rate, 80; respiratory rate, 24	sermann reaction, negative;			pupils, the right larger than the left, and right central facial weakness. Two months later the patient was reexamined and was found to be free from signs and symptoms.	into the subarachnoid space from a ruptured aneurysm is the probable cause. The low blood pressure, as reported here, need not be taken as the normal pressure; a fall as the result of hemorrhage is not unlikely.
35, A. E., 56 years, male, 318165	3 years ago fell on her head; no sequelae; 5 months ago suddenly vomited and complained of severe headache which lasted a week; had a similar attack 4 months previously	Nine days ago for the third time suddenly vomited and experienced pain in the head radiating to the spine; continued to vomit for 4 days	Confused, apathetic and at times psychotic; marked rigidity of neck; bilateral Kernig sign; bilateral papilledema, right greater than left; retinal arteriosclerosis; divergent strabismus; weakness of both internal recti; left pupil greater than right; deep reflexes perhaps slightly more active on right side; abdominal reflexes diminished on right side; right Babinski sign; bilateral absence of pulsations in the dorsalis pedis; blood pressure, 130 systolic and 80 diastolic; temperature, 100 F.; pulse rate, 64; respiratory rate, 28	Xanthochromic; pressure, 200 mm.; Wassermann reaction, negative;	Wassermann reaction, negative	Albumin, faint trace; occasional hyaline cast	A ventriculogram showed symmetrical hydrocephalus. The papilledema persisted. Anomia, perseveration and mental retardation and disorientation developed. On discharge from the hospital 35 days after admission, the papilledema had receded but was still discernible. The ocular palsies were still present. There was a slight memory defect. Two months later the patient was greatly improved. He was amnesic for his stay in the hospital. The positive findings were: generalized hyperreflexia; divergent strabismus; left disk pale. Six months later the status was unchanged, and he was apparently well. He was reexamined on May 1, 1931, 7 months after discharge. He was found to be in good condition, mentally clear and amnesic for his stay in the hospital. Aside from a slight left rectus weakness he had no objective signs.	The patient obviously had had 2 previous attacks of subarachnoid hemorrhage. A ventriculography was performed in order to rule out a neoplasm. It revealed a fairly definite bilateral internal hydrocephalus. The subsequent clinical course excluded the presence of a neoplasm. From our experience with postmortem material, we are convinced that internal hydrocephalus is not infrequent in this condition and is very likely due to partial obliteration of the subarachnoid space by the organizing hemorrhage. This case also presented marked mental disturbances; hallucinations, delusions and ideas of persecution, which persisted for a considerable period of time after the general physical condition showed a decided improvement. An aneurysm due to arteriosclerotic alteration in the cerebral vessels may be safely assumed.
36, C. D., 42 years, male, 318377	Moderate addiction to alcohol	4 days ago, directly following coitus, fainted and remained unconscious for one-half hour; severe headache and vomiting set in	Moderate rigidity of neck; bilateral Kernig sign; peroral and lingual tremor; right knee jerk greater than left; bilateral Babinski sign, left greater than right; generalized arteriosclerosis; blood pressure, 170 systolic and 85 diastolic; temperature, 102.8 F.; respiratory rate, 20	Bloody, under markedly increased pressure; Wassermann reaction, negative;	White blood cells, 11,200; polymorphonuclear leukocytes, 84 per cent; Wassermann reaction, negative	Normal	The cerebrospinal fluid was persistently bloody; it became xanthochromic on the fifth day. There was a gradual improvement. The only positive finding on discharge from the hospital 30 days after admission was an equivocal right plantar response. Two months later the patient was free from signs and symptoms except for occasional headache.	The patient was reexamined on May 1, 1931, 8 months after his discharge from the hospital. He had no complaints. The neurologic status disclosed no positive findings aside from generalized hyperreflexia.

* Ago as used in this table refers to the time elapsed previous to admission to the hos pital.
† The Strauss monometer was used to measure the pressure of the cerebrospinal fluid.

CASE 37.—*Headache, stiffness of the neck and pain in the lumbar region; marked improvement; a furuncle, with pain in the back and rigidity of the neck; recovery.*

History.—C. H., a man, aged 49, who was admitted to the Mount Sinai Hospital on Jan. 1, 1926, eight days before, in the course of a severe emotional stress due to the death of his wife, suddenly experienced the sensation of something snapping in the back of his neck. A few hours later, he felt a sudden pain in the lumbar region of the back and the neck became rigid. The temperature rose to 102 F. The next day he began to suffer from severe headache. Two days later, the temperature returned to normal, but the headache, stiffness of the neck and pain in the lumbar region persisted. On the fourth day of the illness, he complained of pain and frequency of urination, and the family physician reported "blood and pus" in the urine. On the sixth day, the patient became drowsy and at times irrational. The temperature rose again.

Examination.—The patient appeared acutely ill and complained of headache and severe pain in the back. He was drowsy, but could be easily aroused. The tongue was dry and coated; the nasopharynx was congested; moist râles were heard at both bases of the lungs. When roused from the drowsiness, he answered questions correctly and was well oriented for time and place; but he lapsed back to the semistuporous condition immediately when left alone. There were marked rigidity of the neck and a bilateral Kernig sign. The pupils were small but reacted to light and in accommodation. The left side of the soft palate did not move as freely as the right. The deep reflexes were all present and equally active on the two sides, but the abdominal reflexes were diminished on the left side. A smear from the throat showed gram-positive cocci and bacilli. The urine was normal, and the Wassermann reaction of the blood was negative.

Course.—Lumbar puncture on the day following admission yielded clear fluid under normal pressure. The Wassermann reaction of the fluid was negative. Two days later, the temperature rose to 103 F., and lumbar puncture again yielded bloody fluid. A third lumbar puncture, two days later, also yielded bloody fluid. The meningeal signs persisted, and the patient continued to be semistuporous and somewhat delirious. A blood count showed: white cells, 12,000; polymorphonuclear leukocytes, 73 per cent; lymphocytes, 21 per cent; monocytes, 6 per cent.

On the eighth day of residence, the patient began to show remarkable improvement. The temperature became normal, and he became quiet, cooperative and mentally clear. Two days later, a lumbar puncture revealed xanthochromic fluid containing 205 cells per cubic millimeter (mostly lymphocytes). Twelve days after admission, the patient was normal mentally, and of the objective signs there remained only a certain amount of limitation in movement of the head and a slight facial asymmetry.

On the nineteenth day, there developed a large furuncle over the left hip from which pus was expressed. Despite the fact that this was yielding well to treatment, five days later he again had an elevation of temperature to 101.4 F. He complained of pain in the back; rigidity of the neck and a bilateral Kernig sign were elicited. Lumbar puncture yielded turbid fluid containing 760 cells per cubic millimeter, 74 per cent of which were polymorphonuclear leukocytes. A blood count showed: white cells, 17,200, with polymorphonuclear leukocytes, 94 per cent; lymphocytes, 5 per cent; monocytes, 1 per cent. Three days later, another lumbar puncture yielded clear, slightly yellowish fluid under normal pressure, containing 44 cells (mostly lymphocytes).

The patient's temperature continued to be elevated. The throat and pharynx were intensely congested. The frank meningeal signs persisted. On February 3,

thirty-three days after admission to the hospital, a lumbar puncture yielded definitely turbid fluid under increased pressure, containing 1,065 cells, with 80 per cent polymorphonuclear leukocytes. During the next three weeks, six lumbar punctures gave essentially the same results, i.e., turbid fluid under increased pressure containing between 1,000 and 2,000 cells, practically all of which were polymorphonuclear leukocytes. Cultures of the fluid were persistently negative.

At the end of the seventh week in the hospital, though the meningeal signs began to abate, he was given three injections of 2 per cent mercurochrome intravenously. Following the second injection he began to make further improvement, the meningeal signs gradually disappearing. A lumbar puncture on March 10 yielded a slightly yellow fluid under normal pressure; it contained 127 cells, 68 per cent lymphocytes. He was discharged from the hospital on March 14, two and one-half months after admission, free from signs and symptoms.

The patient was observed from time to time in the follow-up clinic, and when last seen on Jan. 23, 1930, appeared to be in excellent condition; examination at this time disclosed no objective signs other than slightly depressed deep reflexes.

Comment.—The diagnosis of spontaneous subarachnoid hemorrhage in the light of the clinical course need not be questioned, for aside from milder deviations the case presented all of the features of this syndrome. However, the true causative factors cannot be readily established, because of several unusual events during the latter part of the clinical course: the recurrence of meningeal signs coincident with the appearance of the furuncle after a period of progressive improvement and the high polymorphonuclear cell count in the cerebrospinal fluid. But, in spite of these atypical observations and coincidences, it is most probable that repeated oozing from a defective vessel was responsible for the series of events.

SUMMARY OF THE CLINICAL OBSERVATIONS, WITH COMMENT

The more important clinical points of interest obtained from an analysis of the records in thirty-four cases are presented in the following tabulations:

Age and Sex Incidence

Youngest, 17 years
Oldest, 68 years
Average age, 31.3 years
Males, 21
Females, 13

Though it would appear from a survey of our material that spontaneous subarachnoid hemorrhage is apparently a disease of middle age, it is equally patent that it may occur at any age. One of us (Dr. Globus) has had under observation a boy of 10 years, who rapidly made an apparently full recovery from a typical attack of spontaneous subarachnoid bleeding and remained well for ten months. He had recently suddenly developed another mild attack with a small amount of blood in the cerebrospinal fluid. He is now convalescing satisfactorily.

Important Events in the Past History.—In evaluating events in the past history as to their value as causative factors, it is essential to discriminate between facts that have but a remote influence and those that have a direct bearing on the anatomic integrity of cerebral blood vessels.

Remote Events in the Patient's Past History

Influenza in 2 cases
Pneumonia in 3 cases
Tuberculosis, pulmonary, in 3 cases
Grip in 1 case
Typhoid in 1 case
Rheumatic fever in 1 case
Alcoholism in 1 case

Direct Events in the Patient's Past History *

Cardiovascular disease in 3 cases
Hypertension in 2 cases
Syphilis in 2 cases
Eclampsia in 1 case

Probable Precipitating Causes

Lifting heavy weight in 2 cases
Coitus in 2 cases
Trauma (fall from height) in 2 cases
Drinking in 1 case
Emotional duress in 1 case

The data as to the probable precipitating causes are too meager to permit definite conclusions. It is, however, obvious that the extrinsic provocative factors are not as important as the intrinsic conditions of the vessels. Nevertheless, the former may not be entirely ignored as important contributories to the essential precipitating cause.

Prodromal Symptoms and Onset

Headache in 25 cases
Vomiting in 18 cases
Rigidity of neck in 14 cases
Rise in temperature in 11 cases
Loss of consciousness in 9 cases
Root pain in 6 cases
Vertigo in 5 cases
Convulsions in 4 cases
Restlessness in 3 cases
Rigidity of extremities in 3 cases
Psychosis or marked mental confusion in 3 cases
Stupor in 2 cases
Diplopia in 2 cases
Photophobia in 1 case
Impaired vision in 1 case
Chills in 1 case

* These events indicate the existence of an acquired general vascular disorder or some systemic disease which tends to impair the integrity of blood vessels.

It is obvious that headache, vomiting and the subjective feeling of rigidity of the neck are among the more common early symptoms in the great majority of cases. Elevation of temperature is also frequent and is a somewhat disturbing element, particularly to one who is not familiar with this syndrome.

The prodromes may take several hours or several days before the full clinical picture is unfolded. When the climax is reached, the patient is suddenly and violently overcome by some explosive event: It is often described as something snapping in the back of the neck, followed by intensive headache, general muscular collapse and rigidity of the neck and the upper part of the spine, often terminating in a partial or a total loss of consciousness.

Objective Neurologic Signs

Meningeal signs
- Rigidity of the neck and Kernig sign in 32 cases

Cranial Nerve Palsies
- Third, fourth and sixth nerves involved in 16 cases

Pupillary Changes
- Inequalities and altered pupillary reflexes, etc., in 17 cases

Changes in the Disks
- Blurred disks in 9 cases
- Papilledema in 6 cases
- Hemorrhagic retinitis in 6 cases

Reflex Alterations
- Generalized hyporeflexia in 12 cases
- Generalized hyperreflexia in 3 cases
- Absent deep reflexes in lower extremities in 3 cases
- Pathologic reflexes (Babinski sign, ankle clonus, etc.) in 13 cases
- Hemiparesis in 1 case
- Sensory changes in 1 case

Among the most prominent objective neurologic manifestations were: the signs of meningeal irritation; palsies of the cranial nerves innervating the extrinsic and intrinsic ocular muscles; variable alterations of the disks, indicating increased intracranial tensions, and generalized hyporeflexia, a common clinical feature, which not unlikely is the result of internal hydrocephalus incident to the reduction of the normal absorption of cerebrospinal fluid.

Of diagnostic importance is the almost total absence of signs pointing to focal disorganization of the central nervous system. In our group there was only one case of hemiparesis.

General Systemic Signs and Symptoms
- Elevation in temperature in 27 cases
- Hypertension in 3 cases
- Herpes labialis in 2 cases
- Generalized adenopathy in 1 case

The dominating feature among the signs of a generalized systemic disorder was the rise in temperature. It may not be present in the beginning, but commonly appears at some stage in the clinical course. It may last only a few days or may continue for periods varying from several days to three weeks. The rise in temperature is intermittent, ranging from a little above 100 to 103.5 F. (fig. 19). A probable explanation for its occurrence is the presence of a foreign protein (blood) in the subarachnoid space.

Laboratory Observations

Cerebrospinal fluid, as obtained on first lumbar puncture:
- Bloody in 23 cases
- Xanthochromic in 6 cases
- Clear in 2 cases
- Wassermann reaction negative in 26 cases
- Wassermann reaction positive in 0 cases

In the two instances in which the first puncture revealed clear fluid, subsequent lumbar punctures yielded bloody cerebrospinal fluid.

Blood:
- Wassermann reaction positive in 1 case
- Wassermann reaction negative in 28 cases
- Leukocytosis in 15 cases
- Polynucleosis in 10 cases

Under leukocytosis are arbitrarily grouped cases in which a count above 10,000 of white blood cells was found. By polynucleosis is understood here a differential count with polymorphonuclear leukocytes above 85 per cent. In connection with these findings, it is interesting to recall the observations of Musser,[8] who reported leukocytosis in experimental bleeding.

Urine:
- Albumin in 9 cases
- Casts in 6 cases
- Sugar in 1 case

The massive albuminuria described by French authors[9] was not noted in any of our cases.

Differential Diagnosis.—The syndrome of subarachnoid hemorrhage must be differentiated from a common form of cerebral hemorrhage, usually called apoplexy; from hemorrhage arising from tumor of the

8. Musser, J. H.: The Leucocytes After Hemorrhage, Am. J. M. Sc. **162**:40, 1921.

9. Widal, F.: De l'hémorrhagie méningée, Presse méd. **2**:412, 1903. Guillain and Vincent: Valeur séméiologique de l'albuminurie dans des hémorrhagies méningées, Semaine méd. **29**:505, 1909.

brain, and from various forms of encephalitis. It differs from apoplexy by the presence of definite meningeal signs, the frequent occurrence of papilledema and paresis of the extrinsic ocular muscles, the protracted and intermittent elevation of temperature and the lack of focal symptoms indicative of a destructive process in the brain itself.

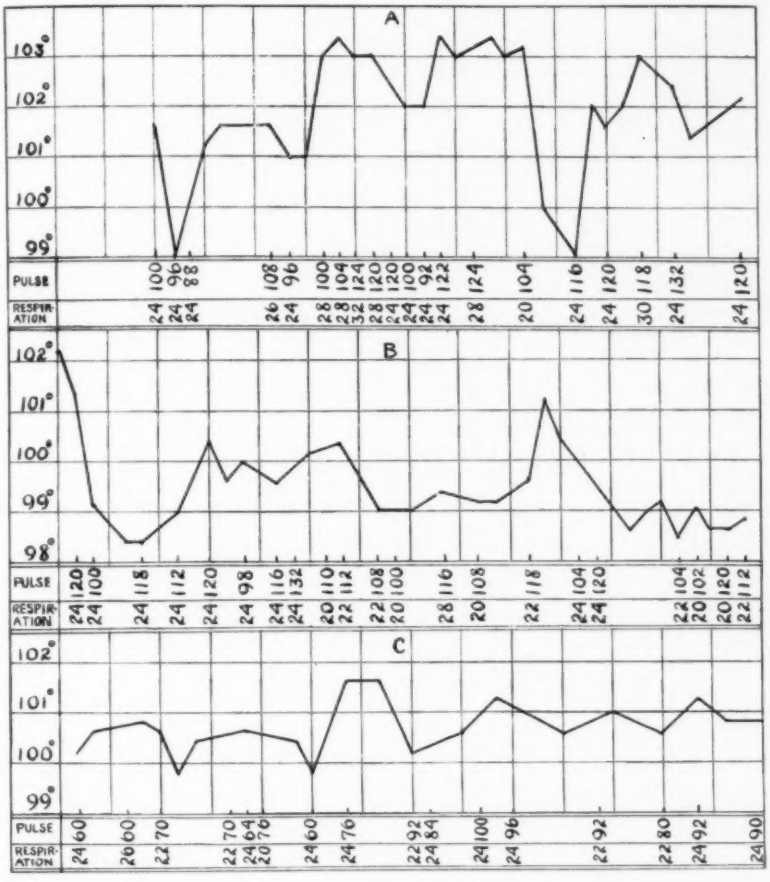


Fig. 19.—Temperature charts: *A*, first week in case 37; *B*, second week in case 37; *C*, first week in case 25 (note the relatively slow pulse).

Hemorrhage into the subarachnoid space from a bleeding tumor of the brain is rare and need not be considered seriously in differential diagnosis. The distinguishing features will become apparent in the later progress of the clinical course.

Encephalitis is often considered in the diagnosis, because of the meningeal signs, rise in temperature, ocular palsies and disturbance of

sensorium common to both conditions. However, the presence of blood in the cerebrospinal fluid establishes the diagnosis of spontaneous subarachnoid hemorrhage, since similar bleeding in encephalitis is a rare occurrence. Furthermore, papilledema is frequently noted in spontaneous subarachnoid hemorrhage, while its development in encephalitis is extremely unusual.

Treatment.—The therapeutic measures employed by us were usually dictated by the clinical demands in the individual case, once the correct diagnosis had been made (the latter offers little difficulty to one familiar with the clinical features of the syndrome). Repeated but guarded lumbar puncture was the most important therapeutic aid. It was carried out cautiously, the fluid being allowed to escape slowly, and only small quantities being removed at a time (from 15 to 25 cc.). At this point we wish to emphasize the importance of slow removal of fluid with the aid of a manometer. If done in this fashion, puncture may be done as often as necessary without fear of renewed bleeding or other untoward effect. It should, however, be done only when indicated by evidence of increased intracranial tension, such as headache, advancing papilledema and a slow pulse rate. Intravenous administration of dextrose is another measure that may be used with benefit. In our experience rigidity of the neck was found to be of little value as an indication for lumbar puncture, as it may remain for a long time after symptoms of intracranial tension have disappeared and the patient is rapidly progressing toward recovery. The patient should, however, not be permitted out of bed for a considerable period until after objective signs have disappeared or markedly diminished and there is freedom from subjective complaints. The spinal fluid must be clear and colorless and the pressure normal (from 90 to 120 mm.) before the patient may be regarded as recovered. A liberal use of sedatives is essential during the early stages to relieve headache and abate restlessness, for it is important to keep the patient quiet. In cases of hypertension chloral hydrate is administered freely but judicially for the reduction of tension and as a sedative.

Final Outcome.—Eleven patients died in the hospital. Twenty-three patients were discharged as recovered. Of the latter, three have died under circumstances suggesting a recurrence of subarachnoid bleeding. Six were recently reexamined and found to have practically no subjective complaints and, in some instances, few residual objective signs. Five, though not available for examination at the time of writing, were, however, periodically examined over periods of from two months to four years from the time of discharge from the hospital. With the exception of one, none of them have complained of disability or have shown alterations in the physical condition. Nine patients could not be reached, and their present condition is unknown.

Time Elapsed Between Patient's Discharge from the Hospital and the Last Examination

5 years and 1 month	1 case
4 years	1 case
2 years and 10 months	1 case
1 year and 7 months	1 case
1 year and 5 months	1 case
1 year	1 case
9 months	2 cases
7 months	1 case
2 months	2 cases

SUMMARY OF ANATOMIC OBSERVATIONS

Of the fourteen fatal cases of spontaneous subarachnoid hemorrhage, eleven were autopsied. In all of the latter, evidence of generalized or focal arteriosclerosis of the cerebral blood vessels was found. In seven, an aneurysm of a cerebral blood vessel apparent to the naked eye was revealed; in four, defects in blood vessels, apparent only on microscopic examination, were found. In two of the latter the altered blood vessels may be considered as microscopic aneurysms. In nine of the eleven cases, alterations characteristic of cerebral arteriosclerosis were found in the brain and smaller vessels. In one case the lesion was that of meningovascular syphilis and in another that of encephalitis and endarteritis associated with subacute bacterial endocarditis. In several cases, arachnoid adhesions were found about the defective blood vessel. It may be assumed that they formed a temporary protective membrane to arrest the escape of blood from the ruptured vessel, and in some instances to prevent the spread of the blood to other areas of the subarachnoid space, limiting it to a circumscribed area. Three cases, in which large aneurysms were present unassociated with massive subarachnoid bleeding were included in this study. In the three instances, local arteriosclerotic changes were found in aneurysmal walls and in parts of vessels adjacent to the aneurysms.

SUMMARY AND CONCLUSIONS

1. Thirty-four cases illustrating the syndrome of spontaneous subarachnoid hemorrhage are described.

2. The term "spontaneous subarachnoid hemorrhage" is limited to massive extravasation of blood into the subarachnoid space, caused by spontaneous rupture of a blood vessel; it excludes hemorrhages into the same space resulting from extension of intracerebral bleeding and minor bleeding in the course of systemic infections, blood disease or those occurring during agonal episodes.

3. The syndrome is characterized by a relatively short prodromal period, in which headache, dizziness, nausea and rigidity of the neck

and spine are the outstanding manifestations. It is followed by an abrupt and explosive onset of the active stage, ushered in by violent headache, partial or total loss of consciousness, and occasionally by convulsions. Examination discloses signs of meningeal irritation (rigidity of the neck, and Kernig and Brudzinski signs), signs of increased intracranial tension (papilledema and depressed reflexes) and often palsies of extrinsic ocular muscles. At this stage the cerebrospinal fluid is usually bloody, occasionally xanthochromic and rarely clear.

4. The clinical course may be short, the patient recovering in the course of several days, or stormy and protracted, lasting over a period of weeks (average in our material, forty-six days).

5. During the clinical course, neurologic and systemic manifestations may develop and disappear. Among the former are intellectual and emotional disturbances, approaching or developing into a confusional psychosis, progressive elevation of the disks, accentuation in the meningeal signs and cranial nerve palsies. Among the systemic manifestations are elevation of temperature, presenting an irregular curve, and leukocytosis.

6. Recurrences of bleeding, with coincident recurrence of signs and symptoms, are not uncommon. They may occur during the initial attack in the character relapses. They may take the form of repeated attacks after a period of convalescence or after an apparent full recovery from a previous episode. Several recurrences may occur before a fatal attack.

7. The recognition of the syndrome of spontaneous subarachnoid bleeding as differing from other forms of intracranial hemorrhage is essential, for the therapeutic indications differ. Treatment for spontaneous subarachnoid hemorrhage consists of repeated lumbar punctures to relieve symptoms of increased intracranial tension. Headache, the mental state, slowing of the pulse and papilledema are the guiding factors determining the need and frequency of this therapeutic measure.

8. The prognosis is always grave, though not hopeless; satisfactory recoveries are frequent.

9. The common anatomic changes are arteriosclerosis of the cerebral blood vessels, with or without frank aneurysmal defects. Inflammatory lesions of blood vessels are also capable of causing aneurysmal formation with ultimate rupture and hemorrhage.

10. Spontaneous subarachnoid hemorrhage may occur at any age (from 10 to 70), though it is most frequent between the ages of 25 and 40.

11. Spontaneous subarachnoid hemorrhage is a disease entity that should be clearly understood not only by the neurologist, but also by the internist, who is more likely to be called on to diagnose and treat the condition in its acute stage.

ABSTRACT OF DISCUSSION

DR. CHARLES BAGLEY, JR., Baltimore: This paper interests me very much as I have had exactly the same experience in patients of this type and published some similar cases in 1928.[10]

In seven of our cases in which autopsies were performed we found a small ruptured aneurysm of the anterior cerebral artery. In one there was a small aneurysm of the left carotid artery, and in another the ruptured aneurysm was found on a small branch of the left posterior communicating artery.

The treatment of patients with spontaneous subarachnoid hemorrhage is a much greater problem than that of patients with bloody cerebrospinal fluid resulting from trauma. The underlying lesion of the vessel is the determining factor. The lack of elastic tissue in a portion of the ruptured vessel in cases of spontaneous hemorrhage results in faulty closure of the wall, a condition that readily permits recurrence of the bleeding. The initial bleeding in some of our cases in which autopsies were performed was sufficient to cause death within a few hours; however, in the majority of cases the fatal secondary bleeding took place within the first month. In one case previously reported there was an interval of twenty years between the first and second bleeding; a large calcification marked the area of the original bleeding. The patient recovered from the second bleeding and died two hours after the onset of the third bleeding, which occurred eighteen months later.

Routine lumbar puncture in these cases is not advisable. The withdrawal of irritating, bloody, cerebrospinal fluid is desirable as a means of diminishing the meningeal irritation and hastening recovery; the main object, however, is to prevent a second and more serious hemorrhage. The authors have expressed the opinion that the rent in the vessel of the patients who recover is sealed by the organization of blood clot. It seems probable that the lowering of intracranial pressure by repeated lumbar punctures may interfere with this organization by encouraging further leakage.

DR. WYMAN RICHARDSON, Boston: I have been interested in this subject since 1925, as I happened to see several cases then. During this period, at the Massachusetts General Hospital there have been sixteen cases of spontaneous subarachnoid hemorrhage in young people without evidence of any other disease. I attempted to follow up the eight cases that occurred four years or more ago: Five patients were followed, two were lost from observation and one died in the hospital; one is well after fourteen years, one after six years and one after five years, and two are well at the end of four years, all without recurrences. The two who have not been followed up may or may not have had recurrences. Of the sixteen patients, three died in the hospital, and autopsies were secured in two cases. In these cases, the cause of the hemorrhage was not discovered in spite of a careful search. That does not mean that there might not have been a ruptured vessel. It was curious, however, that the hemorrhage appeared to be subdural rather than subarachnoid.

In studying the symptomatology in this group of cases, our experience, in general, has been exactly the same as that of the previous speaker. There does seem to be, however, at least in this small group of cases, occasionally a different mode of onset, which is more insidious and which occurs in relation to a coincident infection of the upper respiratory tract. It so happens that both the cases in which autopsies were performed were of this type. It seemed to me conceivable

10. Bagley, Charles, Jr.: Blood in the Cerebrospinal Fluid: Resultant Functional and Organic Alterations in the Central Nervous System, Arch. Surg. **17**:18 (July) 1928.

that there might be a different process involved. Most of the cases, however, showed the sudden onset of headache or coma described by the presenters.

In regard to hypertension, it is difficult for me to be certain whether it existed before the hemorrhage. Recently there has been a case with definite hypertension following the hemorrhage in which the blood pressure returned to normal limits with the reduction of intracranial pressure following lumbar puncture.

In speaking of massive albuminuria, there have been several patients in the group of sixteen who showed large amounts of albumin and who did not appear to have renal disease, and it occurred to me to wonder whether there might not be a central control of albumin excretion similar to the control of sugar excretion and whether a certain definite injury in the brain might not result in albuminuria similar to the glycosuria seen in certain such injuries.

Dr. Arvid Lindau, University of Lund, Sweden: There are perhaps a good many aneurysms that might be considered. There are a certain number of patients who have earlier partial ruptures from scars in the connective tissue. My countryman Reuterwall examined the brain in a large area and found the same lesion in the wall of an artery. These weak arterial points may be the origin of some of the aneurysms. Perhaps some of the cases shown by Dr. Bagley, in which there was an absence of inflammatory change, might be of this origin.

We have observed in Sweden several cases in which there were albuminuria and also a high nonprotein value in the blood. It is rather interesting that the late Professor Petren, an honorary member of this Society, observed a case in which the patient had subarachnoidal hemorrhage twice and on both occasions the nonprotein value in the blood was higher than 100. This suggests, as the last speaker said, a possible central origin of this type of albuminuria and high blood protein.

Dr. Israel Strauss, New York: In our paper we have referred to the work of Dr. Lindau's countryman.

Regarding the rupture, we have not been able to prove anything of the kind, but it is plausible that ruptures may occur in arteriosclerotic vessels without aneurysm.

We do say that we are able to relieve intracranial pressure, as indicated by severe headache, increasing papilledema and a slow pulse, by lumbar puncture.

One other important point is that the patients at times give a history indicating the presence of a sudden hemorrhage.

SPONTANEOUS CEREBRAL HEMORRHAGE

DISCUSSION OF FOUR TYPES, WITH SURGICAL CONSIDERATIONS

CHARLES BAGLEY, JR., M.D.
BALTIMORE

An accumulation of interesting specimens showing various types of lesions after spontaneous rupture of cerebral vessels has prompted the writing of this report. The purpose of the paper is to describe four types of spontaneous hemorrhages classified according to the clinical and postmortem observations in twenty cases and to outline the surgical treatment of the types that can be benefited by lumbar puncture or operation. Cases of spontaneous bleeding in cerebral tumors are not included in these types. The great problem, of course, lies in the correct diagnosis, so that the occasional surgical cases may be picked from the large group of apoplexies. The selection of cases can be facilitated by dividing them into types based on the clinical findings so as to be of service at the bedside.

Interest in the symptomatology of cerebral bleeding has been gradually increasing since the publication of papers by Symonds [1] and Cushing [2] in 1923. One must first differentiate between the meningeal and the intracerebral types of bleeding, and these two groups must be divided again; the meningeal group being divided according to whether there is a small or large amount of blood in the cerebrospinal fluid, and the intracerebral according to the location of the clot, that is, whether it is near the surface or deep in the substance, causing irreparable destruction which will only be increased by surgical attack.

The grouping is based chiefly on the symptomatology of meningeal irritation in the meningeal bleeding and on the signs and symptoms of increased intracranial pressure in intracerebral bleeding.

The following grouping serves as a working clinical basis, and the postmortem observations justify this simple division of the cases.

Submitted for publication, Jan. 1, 1932.

From the Neurological Laboratory of the Henry Phipps Psychiatric Clinic, Johns Hopkins University.

Read at the Forty-Fourth Annual Session of the Southern Surgical Association, Dec. 9, 1931.

1. Symonds, C. P.: Clinical Study of Intracranial Aneurysms, Guy's Hosp. Rep. **73**:139 (April) 1923.

2. Cushing, H.: Clinical Study of Intracranial Aneurysms, Guy's Hosp. Rep. **73**:159 (April) 1923.

Group 1.—Meningeal Bleeding.

Type A: A small or moderate amount of bleeding, the blood being thoroughly mixed with cerebrospinal fluid. The symptoms are irritative or meningeal in character.

Type B: A large amount of bleeding, with the formation of a clot. The meningeal symptoms are overshadowed by signs of pressure. Patients in this group frequently present first the symptoms listed under type A, but the initial bleeding may be large enough to place them in this group directly.

Group 2.—Intracerebral Bleeding.

Type C: Large clots, deep in the substance of the brain, with extensive destruction and usually complete hemiplegia.

Type D: Bleeding into the cortex with signs of increased intracranial pressure which may appear suddenly or progress gradually, according to the volume of bleeding. Focal symptoms may or may not be present.

The following cases are presented as examples of the various types.

MENINGEAL BLEEDING

GROUP 1.—TYPE A

A small or moderate amount of blood escapes and is washed into the cerebrospinal fluid, producing the characteristic bloody cerebrospinal fluid. This type may be described as follows: The patient complains of pain beginning in the suboccipital region and extending within a few hours over the entire head. Vomiting usually occurs early, and is likely to continue. There are leukocytosis, mental confusion and delirium of a varying degree. The temperature is elevated, but is rarely above 102 F. rectally; if the amount of the blood is small, it may not go above 101 F. The pulse is quickened, the rate ranging from 90 to 120. Postcervical rigidity and a positive Kernig sign are present after the first forty-eight hours. In some cases the blood will be absorbed and all the symptoms will gradually disappear during a period of two weeks.

Lumbar puncture within a few hours shows a mixture of blood and cerebrospinal fluid, the richness of the mixture depending on the amount of bleeding. The blood will not coagulate in a test tube. In cases in which only a small amount of blood escaped into the fluid and there was no subsequent bleeding the fluid may have a yellowish tinge as early as twenty-four or forty-eight hours after the onset of the bleeding. In cases of this type the fluid will probably be entirely clear within two weeks. If the patient is unable to absorb the blood and a lumbar puncture is not done, there are gradually increasing symptoms; the patient becomes wildly delirious, headache and vomiting are very troublesome, the temperature is still elevated, and the pulse rate is high.

In the majority of cases, however, either the oozing continues or there is recurrent bleeding so that the fluid is blood stained for several

days. In cases of recurrent bleeding the yellow fluid again becomes blood stained. Where there is a small amount of bleeding the cerebrospinal fluid pressure is not increased above normal and may even be low, while in the severer cases of this group it is usually very high in the beginning, rapidly returning to a normal level with other signs of improvement. The ophthalmoscopic findings vary from slight edema of the disks in the mild cases to definite elevation and obscuration of the margins, and not infrequently retinal hemorrhages in the severe cases.

This type includes the most favorable cases. I shall not attempt in this report to tabulate a number of these cases that have come under observation, but will present three cases illustrating degrees of severity in patients of this type. In case 1 the symptoms were characteristic in their onset and progress, and cleared up satisfactorily following occasional lumbar puncture. Case 2 presented more serious symptoms than case 1, and recovery took place following occasional lumbar puncture. The patient in case 3, with a similar course, died seventy days after the meningeal bleeding, following a severe hemorrhage from the kidney. The ruptured cerebral vessel was found partially healed, presenting a good example of what takes place in cases of recovery.

REPORT OF CASES

CASE 1.—*Evidence of chronic systemic infection from the teeth and tonsils. Sudden onset of meningeal bleeding with gradually increasing symptoms for one week. Slow recovery after two lumbar punctures.*

J. S., a married woman, aged 33, was admitted in a semiconscious condition to St. Agnes Hospital on the service of Dr. Thomas S. Bowyer. She had previously been treated for arthritis. The teeth were examined roentgenologically and some were removed; one week before this admission the patient had a tonsillectomy because of repeated attacks of tonsillitis. The operation was uncomplicated and the patient left the hospital in good condition. Twenty-four hours after leaving the hospital, she had a convulsion and was unconscious for one hour. Following this there was a severe headache and the patient was dull. The systolic blood pressure during the week was 140 mm. of mercury. Six days after the convulsion she was admitted to the hospital and the systolic blood pressure was 200 mm. of mercury. The headache was severe, chiefly in the frontal region, and was accompanied by stiffness of the neck and a positive Kernig sign. The eyegrounds showed beginning choking, with numerous small retinal hemorrhages. A lumbar puncture showed xanthochromic cerebrospinal fluid. Following the puncture there was gradual improvement in the symptoms. A second lumbar puncture, done a week later, showed the fluid to be only slightly xanthochromic. The symptoms gradually disappeared, and the patient was discharged from the hospital eighteen days after admission.

It is now more than a year since her discharge, and there has been no recurrence of the symptoms. The patient is carrying on her housework, and has no complaint other than peculiar sensations in the head which she describes as a numbness or burning, but no definite headache. The systolic blood pressure at the time of the last examination was 120 mm. of mercury.

CASE 2.—*Severe recurrent bleeding, the lesion probably an aneurysm; cephalic bruit after recovery.*

W. I. V., a married man, aged 50, stated that his only serious previous illness was a ruptured appendix with peritonitis six years before, when he remained in the hospital for ten weeks and finally made a good recovery. Three weeks before the present illness he had complained of pain in the chest, which was diagnosed as intercostal neuralgia. The blood pressure at that time was 170 systolic and 100 diastolic. A week later, the blood pressure was 166 systolic and 90 diastolic. The patient was overweight and for years had worked for long hours, usually finishing about 10 p. m., after which time it was his regular habit to take several drinks of whisky and eat a heavy meal.

The present illness began suddenly at 10 p. m., when he was found lying on the floor of the bathroom in his home in an unconscious state. About three hours later, he was admitted to St. Agnes Hospital, where I saw him in consultation with Dr. James G. Howell and Dr. Irvin J. Spear.

At the time of admission, he was still unconscious; his breathing was stertorous, the face was flushed, the blood pressure was 120 systolic and 60 diastolic, the pulse rate was 88, the temperature was 99.4 F. and the pupils were sluggish and equal. On the following day, the patient was still unconscious; the reflexes were present throughout; the blood pressure was 120; the Kernig sign was positive on both sides, and the neck was rigid. Forty-eight hours after admission, he began to arouse, and complained of very severe headache; on the following day he was conscious but disoriented and confused, and the blood pressure was 160 systolic and 90 diastolic. Ophthalmoscopic examination showed slight edema of the disks. The cerebrospinal fluid obtained by a lumbar puncture contained a large amount of blood, which was well mixed with the fluid, the color being bright red. The cerebrospinal fluid pressure was not recorded. There was suggestive weakness of the right side of the face and tongue, and all the deep and superficial reflexes were active. On the following day the patient complained of a severe headache, was restless and quite disoriented, and insisted on getting out of bed; a little later, however, he was somewhat cooperative and recognized his wife. Because of the severe headache a second lumbar puncture was done; the fluid obtained showed a remarkable decrease in the amount of blood, indicating that a great deal of the blood had been absorbed since the lumbar puncture twenty-four hours previously. The cerebrospinal fluid pressure at this time was 390 mm. of water. Following the puncture the patient was more comfortable.

Thirty-six hours later, he had a severe headache, became very delirious and restless; within a few hours his condition seemed very grave, and a third puncture was done. It showed a very high degree of pressure, the reading of which could not be obtained above 300 because of an accident to the manometer. The fluid withdrawn was much more bloody than that obtained on previous punctures, so it was believed that the patient had had a recurrent hemorrhage during the night. Following the puncture he was quieter for two or three hours, but at this time the delirium became troublesome; the patient was very talkative and had a severe headache, and the blood pressure was 210 mm. of mercury. Because of the sharp

rise of the blood pressure, 200 cc. of blood was removed from a vein in the arm, and the pressure immediately dropped to 130. One and one-half hours later, the blood pressure was 165, but the patient's condition seemed improved. On the following day, he was restless and uncomfortable, and the blood pressure remained between 160 and 170; 50 cc. of 25 per cent dextrose solution was given intravenously. For forty-eight hours the patient gradually improved and was semiconscious. From this time improvement continued; the patient was talkative but entirely cooperative, and gradually became well oriented.

A week later, he was still very talkative and inclined to exaggerate. He realized that he had been sick and wanted to discuss his previous habits of eating, fearing that his bad habits of eating and drinking were responsible for the illness, and at the same time wanting to make sure that he would not be obliged to curtail them. He began to recall events immediately preceding the attack; he remembered eating a large fish dinner one hour before, and that the fish had been caught by a friend earlier in the day. During his delirium he had been particularly concerned about a pet dog, anticipating putting her in a show, but he now realized that the dog had been dead for four years. Throughout this week he had very little headache, was not stuporous and slept normally. He was discharged from the hospital twenty-two days after the onset of the illness to recuperate at home.

Examination at the time of discharge showed active deep reflexes in both upper and lower extremities, a negative Babinski sign, a definitely positive Kernig sign on both sides and some postcervical rigidity. Ophthalmoscopic examination showed obliteration of the margins of the disks and small retinal hemorrhages in both eyes. The mental condition of the patient has continued to improve and he is free from headache. The fluid at the time of discharge was no doubt still xanthochromic, and the pressure was perhaps slightly increased. Further punctures were deemed inadvisable because of the likelihood of precipitating additional bleeding.

Convalescence can no doubt be shortened by repeated punctures, but time must be allowed for the healing of the vessel whether the bleeding is due to rupture of a small aneurysm or an arteriosclerotic wall, as illustrated in this paper. On this point the treatment of these patients differs from that of patients with bloody cerebrospinal fluid following trauma when there has been a rupture of a normal vessel. The injured vessel will be occluded early because of the normal wall structure.

Examination of the patient a month after discharge showed a systolic blood pressure of 140. He complained of very slight bitemporal headache, which was usually present in the morning, and in the right temporal region there was a very soft bruit synchronous with the pulse. This bruit was not heard while the patient was in the hospital, but was distinctly heard two weeks after his discharge. He returned to light duty and was quite comfortable until he contracted a bronchitis with severe coughing which has continued for three weeks. In spite of this, however, there has been no return of the cerebral symptoms. Six months later the bruit disappeared.

CASE 3.—*Moderate amount of blood in the cerebrospinal fluid; improvement in the neurologic condition after lumbar puncture and subtemporal decompression. Fatal hemorrhage from kidney seventy days after meningeal bleeding; healed rupture of the left internal carotid artery found at autopsy.*

L. E. B., a married man, aged 40, was admitted to the Mercy Hospital to the service of Dr. Maurice Pincoffs. He had had scarlet fever, diphtheria and measles in childhood, and also several attacks of quinsy. Five years before admission, he had a very severe sore throat, which was followed by pleurisy and what was

thought to be a septic infarct in the right kidney. About five weeks after the onset of the illness, he had six convulsions and was delirious. Four months after the beginning of the illness, he had seven convulsions, followed by serious impairment of vision. Six months after the beginning of the illness, the patient was admitted to the Roosevelt Hospital, New York, when his physical condition seemed desperate. He was emaciated, weighed only 119 pounds (54 Kg.) and was practically blind. There was occasional twitching of the muscles of the extremities and trunk. Ophthalmoscopic examination showed advanced retinitis, with recent hemorrhages and white patches, and the outline of the disk was completely lost. There was cardiac enlargement, with a rapid pulse rate, a systolic murmur to the left of the sternum, and a blood pressure of 240 systolic and 140 diastolic. Examination of the lungs and abdomen revealed nothing abnormal. The Wassermann reaction of the blood was negative, and examination of the blood showed a moderate anemia; the blood urea was 51 mg. per hundred cubic centimeters. The condition gradually improved under treatment during two months in the hospital. The follow-up record of the hospital covered a period of more than three years. The patient returned to work in five months after discharge and continued until the present illness. A final note on the follow-up record stated that the eyes were almost normal, the blood pressure was 145 systolic and 90 diastolic and the patient was very well and carrying on his regular duties.

Shortly before the patient's admission, a severe headache suddenly developed, and he complained of tingling in both arms. Delirium soon followed the headache, and when he was admitted a few hours after the onset he was disoriented, restless and talkative, and had to be restrained. There was a history of an accidental fall to the floor three weeks before admission, when the patient struck his knee and shoulder, but did not strike his head; there were no neurologic symptoms following the incident. Examination at this time showed a well developed and well nourished man, in a stupor alternating with restlessness, but he could be aroused. There was no paralysis, but the neck was rigid; the deep reflexes were active and the Kernig sign was positive. There was a positive Babinski sign on the right and a suggestive appearance on the left. Both pupils were rather large, the right a little larger than the left, and both reacted sluggishly. On admission the pulse rate was 65; twenty-four hours later, it ranged from 88 to 110, and there was a moderate elevation of temperature. The leukocyte count was 15,600 per cubic millimeter; the red cells numbered 4,480,000, and the hemoglobin was 85 per cent. A lumbar puncture revealed very bloody cerebrospinal fluid. Twenty-four hours after admission, a second lumbar puncture revealed bright red cerebrospinal fluid. During the first nine days after admission, four lumbar punctures were done, and a small amount of fluid was removed. The fluid gradually became less bloody, and on the ninth day was yellow tinged. At this time the patient was still drowsy and confused, and the neck was stiff, but the mental condition was improved.

Eighteen days after admission, the fluid was clear and only slightly xanthochromic, but the patient was in a deep coma; respirations were of the Cheyne-Stokes type; the blood pressure was 170 systolic and 70 diastolic; the pulse rate was 120 to the minute. This condition was believed to be due to cerebral edema and a right subtemporal decompression was done by Dr. Alexius McGlannan. There was gradual improvement in the condition, when suddenly, twenty-seven days after the subtemporal decompression, there was profuse hematuria. There were recurrent hemorrhages into the bladder; nine days after the first evidence of blood in the urine, the patient had a severe hemorrhage and transfusion was done. The hematuria continued and the patient's general condition became more unfavorable; he died twenty-five days after the onset of the hematuria, following a severe hemorrhage. During this period there was no indication of further cerebral bleeding.

Autopsy showed fibrous adhesions at the base of the right lung and at the apex and base of the left lung. The abdomen contained about 300 cc. of free fluid; the liver was enlarged; the kidneys were large and pale; the pelves and ureters were dilated and filled with blood. There were two large cavities in the right kidney substance, one filled with blood clot and the other with fresh blood. The left kidney was large, but did not contain any extravasated blood. The brain appeared normal except for some adhesions at the site of the decompression and yellow staining of the meninges, particularly at the base and extending up over the cortex. Macroscopically, the vessels did not appear atheromatous. After fixation in formaldehyde, a block was removed from the base of the brain, extending from the

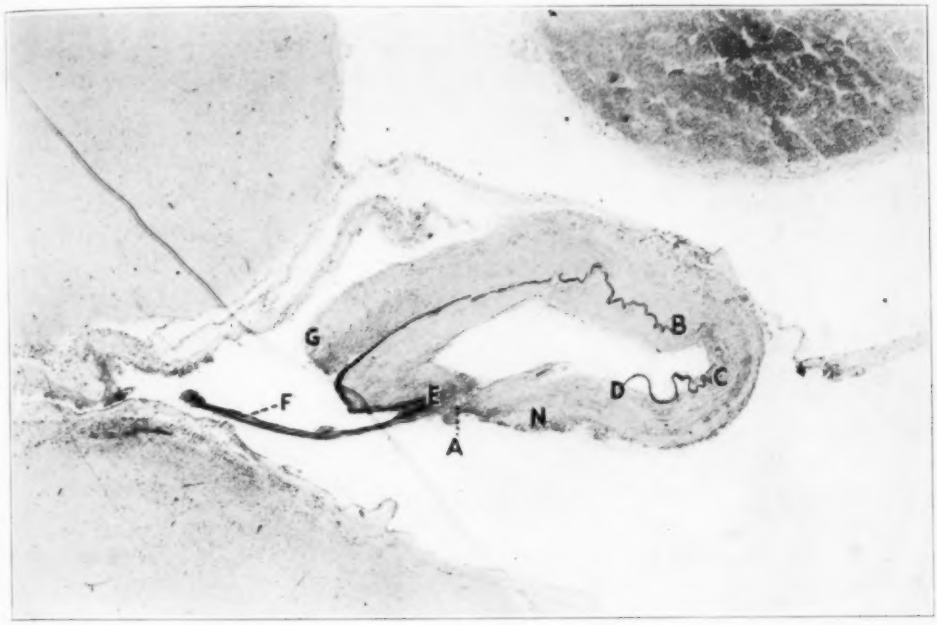


Fig. 1 (case 3).—Section of the left carotid artery showing a rupture which has healed at *A*. The elastic tissue is absent between *B* and *C* and between *D* and *E*. At *F* there is a portion of the wall containing a narrow strip of elastic tissue which originally extended from *D* to *E* but was torn out at the time of the rupture. The external coat is missing between *G* and *H*. Reduced from × 12.

chiasm backward to the interpeduncular space, and sectioned serially. This block was taken with a view to including the circle of Willis and its branches for some distance. Microscopically, there was a moderate thickening of the meninges, which was more marked at the base. In this tissue there were numerous pigment-loaded cells; in the sulci the same thickening of the meninges was noted, with a rich distribution of pigment-loaded cells. The vessel walls varied from perfectly normal ones to those showing slight arteriosclerotic changes, and still others showing very marked arteriosclerotic changes.

The left internal carotid artery is shown in figure 1. The photograph was made from a serial section and shows the vessel at the point of rupture. The rent has healed so that the continuity of the wall has been reestablished and the vessel is patent.

Healing was accomplished in spite of the complete absence of a portion of the outer coat, and with a large part of the elastic tissue remaining outside the healed wall.

There is no evidence of aneurysmal formation in the serial sections of this lesion, and it is therefore shown as an example of direct rupture of an arteriosclerotic vessel. It is of further interest in showing the possibility of healing of a large vessel after rupture. This photograph represents the condition of the vessel seventy days after the sudden onset of the bleeding, and one can only speculate as to what would have happened if the patient had not died as a result of the renal lesion. Three things in the further life of the vessel seem possible: more complete healing, further rupture, or an aneurysmal formation because of the absence of the elastic tissue layer.

GROUP 1.—TYPE B

The symptoms in this type are similar to those in type A, but owing to the escape of a large amount of blood they are more severe, and the evidences of meningeal irritation may be overshadowed by the signs of increased intracranial pressure. The blood escapes beneath the pia-arachnoid, over the cortex, after rupture of the membrane or into the substance of the brain, sometimes reaching the ventricle.

The symptoms vary somewhat according to the location of the extravasated blood. Convulsive seizures and loss of consciousness are the rule immediately after the outpouring of a large amount of blood. If the blood escapes beneath the pia-arachnoid without clot formation one sees the symptomatology described in type A in a more severe form. If there is an accumulation of blood at the base of the brain there is marked disturbance of the thermoregulatory and cardiorespiratory centers, producing an excessive rise of temperature and a very rapid pulse and respiratory rate.

When the blood escapes into the brain substance a clot is formed; there are signs of increased intracranial pressure and perhaps focal neurologic disturbance, dependent on the site of the clot. Thus, by studying the train of symptoms one may form an idea as to the meningeal or intracerebral type of bleeding, a matter of great importance in prognosis and treatment. The excessive bleeding, which is characteristic of this type, may occur primarily and the patient succumb immediately, or a serious outpouring may occur in a patient who is running a type A course. In most of our cases the recurrent bleeding has followed within a few days after the initial slight bleeding, but in one patient whose case was previously reported there was an interval of twenty years.

REPORT OF CASES

CASE 4.—*Small amount of meningeal bleeding; six days later, recurrence of bleeding with more severe symptoms; on the tenth day a large hemorrhage, followed by convulsion and death. Autopsy showed ruptured aneurysm of the anterior cerebral artery.*

F. H. S., a married man, aged 51, complained of a queer feeling in his head while lying in bed early in the morning. A few minutes later, he was nauseated

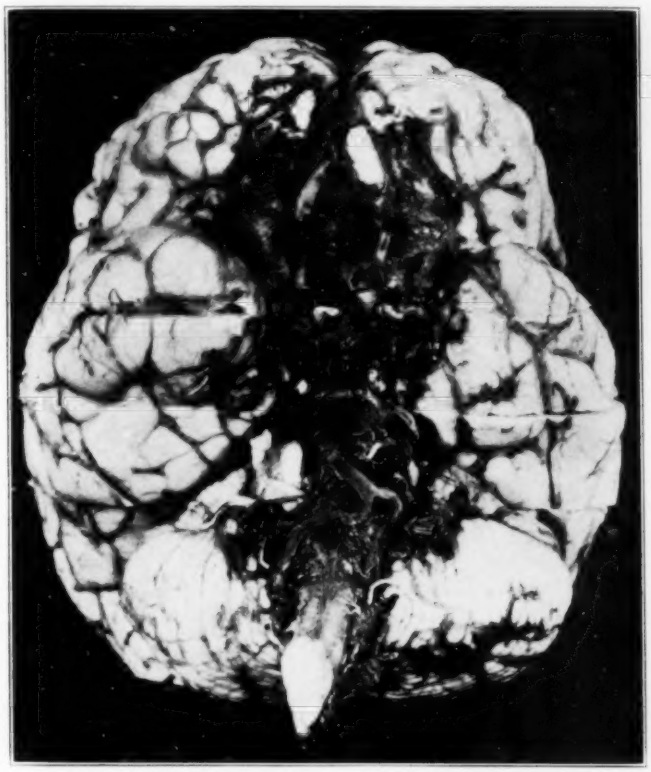


Fig. 2 (case 4).—This brain presents the characteristic picture of extensive subarachnoid extravasation at the base following a fatal rupture of an aneurysm of the anterior cerebral artery.

and complained of headache. The condition gradually progressed and, five days later, I saw him in consultation with Dr. Eldridge E. Wolff, when a lumbar puncture revealed slightly bloody cerebrospinal fluid. Twenty-four hours later, while straining at stool, he complained of a severe pain in the head, had a convulsion and sank into coma. Four days following this, he had another attack and died one hour later in a severe convulsion.

Autopsy showed hemorrhagic extravasation along the base of the brain, more intense at the base of the right frontal lobe, as shown in figure 2. A frontal section of the brain showed the characteristic bursting of this type of hemorrhage

into the lateral ventricle, and serial sections through the hemorrhagic area revealed an aneurysm of the anterior cerebral artery (fig. 3).

CASE 5.—*Extensive skin burns followed after several months by severe meningeal bleeding, with progressing symptoms till death on the thirteenth day. At autopsy, rupture of aneurysm of anterior cerebral artery, probably secondary to bacterial infection in the suppurating wounds.*

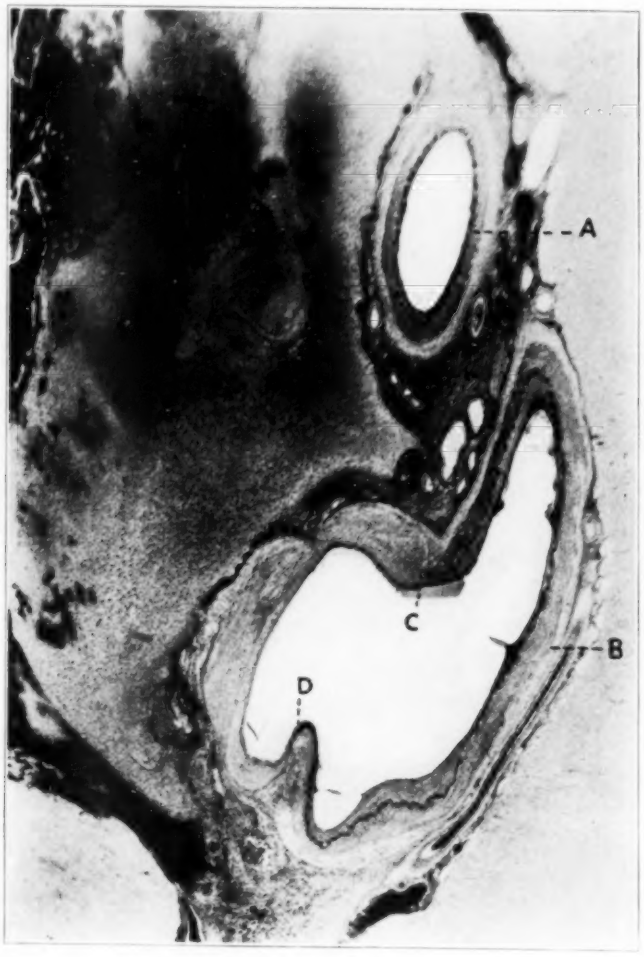


Fig. 3 (case 4).—A section from the brain shown in figure 2. The normal left anterior cerebral artery is shown at *A*, and the right anterior cerebral artery at *B*. The right artery is dilated, and there is a break in the elastic tissue which extends from *C* to *D*; beyond this the aneurysm extends. The bulging portion of the vessel is entirely lacking in elastic tissue. Reduced from × 8.

P. P., a married man, aged 28, was admitted to the Mount Hope Sanitarium on the service of Dr. Charles Hill, where he was seen by my associate, Dr. Richard G. Coblentz. Seven months before admission to the hospital, he had suffered

severe burns as the result of an explosion in the plant where he was working. This necessitated his remaining at the hospital for four months. Following discharge from the hospital, he was restless and irritable, suffered with insomnia and occasionally fainted.

Five days before admission, he was suddenly seized with a severe pain in the back of the head, which was almost immediately followed by a convulsion. Three hours later, there was another convulsion. Restlessness and delirium became more marked, and continued until three days after admission, when the patient was in a deep coma. The temperature after admission to the hospital ranged above 103 F., and a few hours before death was 108.5 F. by axilla. The pulse rate was rapid; the blood pressure was 118 systolic and 90 diastolic; the specific gravity of the urine was 1.033, and there was a trace of albumin; the cerebrospinal fluid was of dark amber color. The patient died eight days after admission.

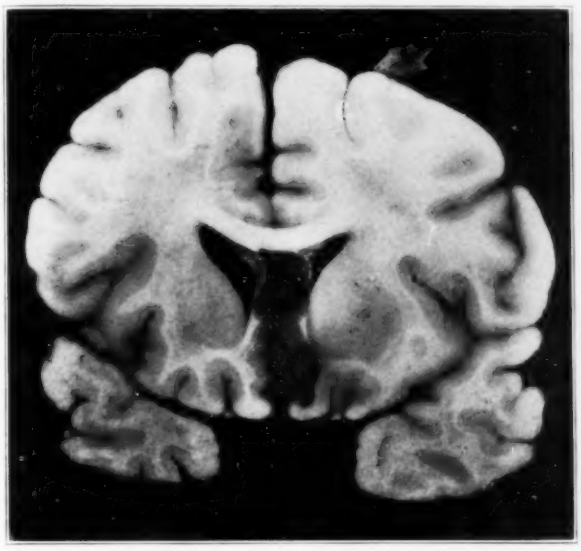


Fig. 4 (case 5).—A hemorrhage into the septum pellucidum secondary to a rupture of an aneurysm of the anterior cerebral artery.

Autopsy revealed a moderate degree of staining of the entire cerebral cortex and moderate thickening of the meninges.

A frontal section through this brain is shown in figure 4. Between the frontal lobes and extending into the septum lucidum there is a firm blood clot which extended upward during the severe bleeding at a time when a great deal of blood escaped into the subarachnoid space. The source of this bleeding was found to be an aneurysm of the anterior cerebral artery, which had ruptured.

In considering the cause of this aneurysm one thinks of a congenital muscularis defect because of the age of the patient. However, the absorption of toxin or direct bacteriologic action on the wall of the vessel secondary to the long-continued suppurating condition of the skin must also be considered as a probable causative factor in the formation of the aneurysm.

CASE 6.—*Rather severe initial bleeding; gradual improvement until a second bleeding on the seventh day with less serious symptoms; severe bleeding on the fourteenth day, followed immediately by death. Autopsy revealed a ruptured anterior cerebral artery.*

H. B. L., a married woman, aged 60, complained of a severe headache, and immediately had a number of convulsions which were followed by stupor. The

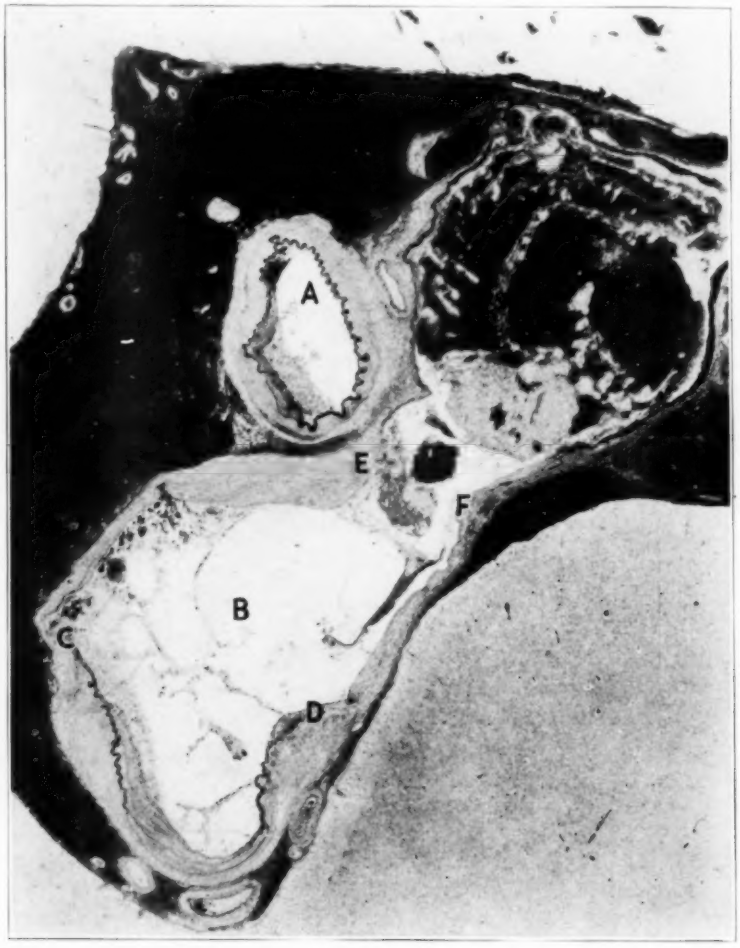


Fig. 5 (case 6).—The right anterior cerebral artery at *A*, and the left artery at *B*, with its elastic coat extending from *C* to *D*. Beyond this the aneurysmal sac, entirely lacking in elastic tissue, extends from *E* to *F*, where it is ruptured. Reduced from × 8.

pulse rate was quick, and the temperature was elevated as high as 100.8 F. There was a gradual improvement for a week, during which the patient had a severe headache; one week later, there was a similar but less severe attack, when lumbar

puncture revealed blood-stained fluid. At this time I saw her in consultation with Dr. Armfield F. Van Bibber. Two weeks after the onset, there was a severe attack, and the patient died about one hour later.

Autopsy showed a large amount of blood over the cortex and a rupture of the cortex at the base of the frontal lobe through which a clot was protruding. There

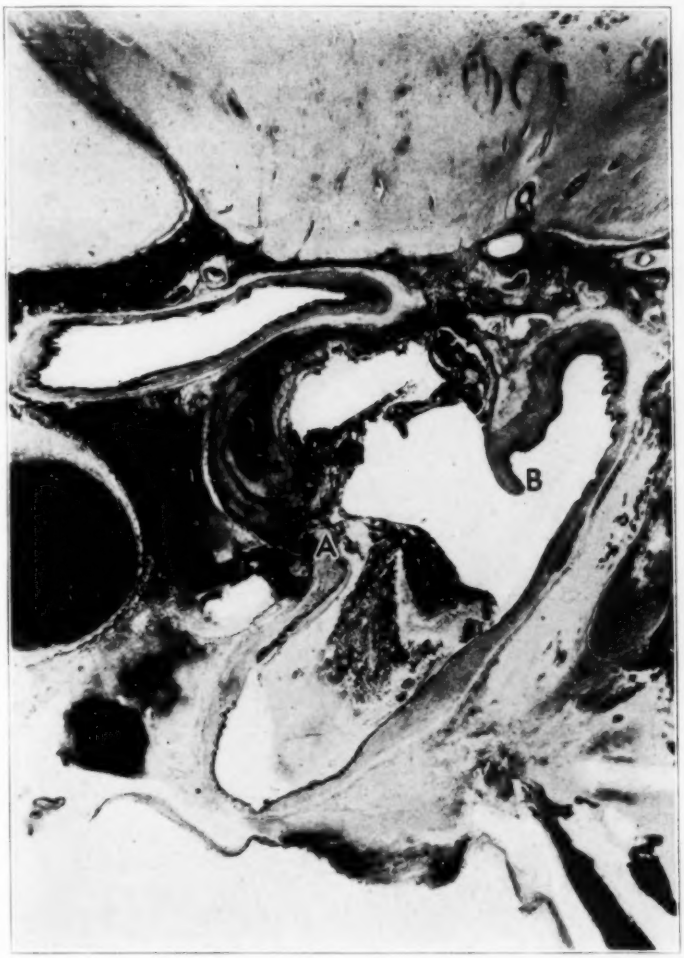


Fig. 6 (case 7).—Middle cerebral artery with the aneurysmal dilatation, the elastic fiber coat of the wall extending from *A* to *B*. Beyond this the thin sac does not contain elastic tissue. Reduced from × 10.

was a large amount of blood at the base of the brain in the neighborhood of the chiasm, but no blood had reached the ventricles. Serial sections through the area of the clot were made, and the diseased left anterior cerebral artery was found, as figure 5 clearly demonstrates. The original vessel wall can be outlined by the

elastic tissue lamina, which ends abruptly at *C* and *D*. Extending from this is the definite aneurysmal sac, which is ruptured. Immediately beyond the point of rupture is the partially organized clot, representing the blood that escaped in the initial bleeding, and beyond this a large hemorrhage which occurred at the time of death.

CASE 7.—*Moderately severe initial symptoms; ten days later, very severe symptoms, including hemiplegia; on the sixteenth day, recurrence of bleeding followed by a convulsion and death. Autopsy revealed small ruptured aneurysm of the internal carotid artery.*

S. G., a married woman, aged 41, was seen in consultation with Dr. W. M. Stirling and was admitted to the Union Memorial Hospital ten days after the onset of the present illness. The past history was unimportant, except for persistent frontal headaches. The initial symptom was severe frontal headache, which radiated to

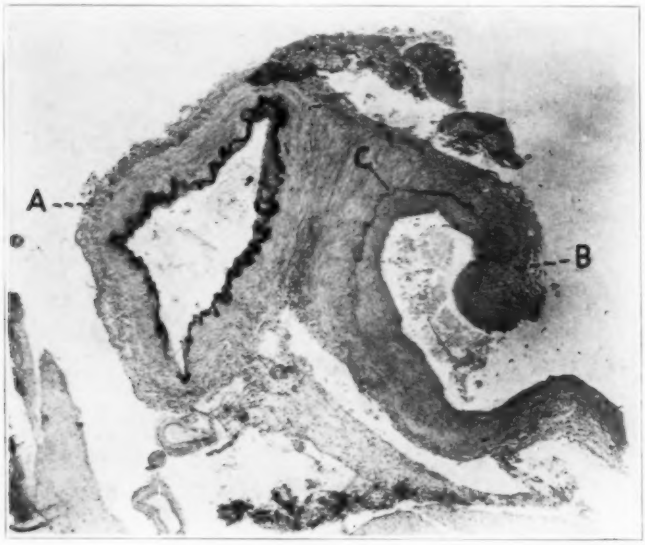


Fig. 7 (case 8).—At *A* the left posterior communicating artery; at *B* a branch of this artery in which there is a small remnant of the elastic tissue at *C*. The wall of the artery is ruptured; × 30.

the occipital region and down the spine; this was followed by sudden loss of consciousness which lasted for two days. On the third and fourth day, she is said to have fainted, but was unconscious for only a few minutes. Just before admission, all the symptoms were more severe, and the patient was admitted in a state of coma, with marked rigidity of the neck and flaccid paralysis of the left side of the body. The blood pressure was 140 systolic and 84 diastolic on admission, and the pulse rate was slow. A lumbar puncture showed deeply blood-stained cerebrospinal fluid. The patient remained in coma, with a slow pulse, and on the following day the blood pressure was 160 systolic and 85 diastolic. Four days after admission, she had a severe convulsive seizure, which was associated with twitching of the right side. Following this the breathing was labored, and the condition seemed more unfavorable. Six days after admission, there was another severe convulsion and the patient died.

Autopsy showed a large amount of blood at the base of the brain, extending over the cortex on both sides. In addition to this free blood there was a large amount of blood in the pia-arachnoid mesh of the entire brain, giving a very dark appearance. After fixation in formaldehyde, the brain was cut transversely and showed the ventricles filled with blood. Serial sections through the base of the

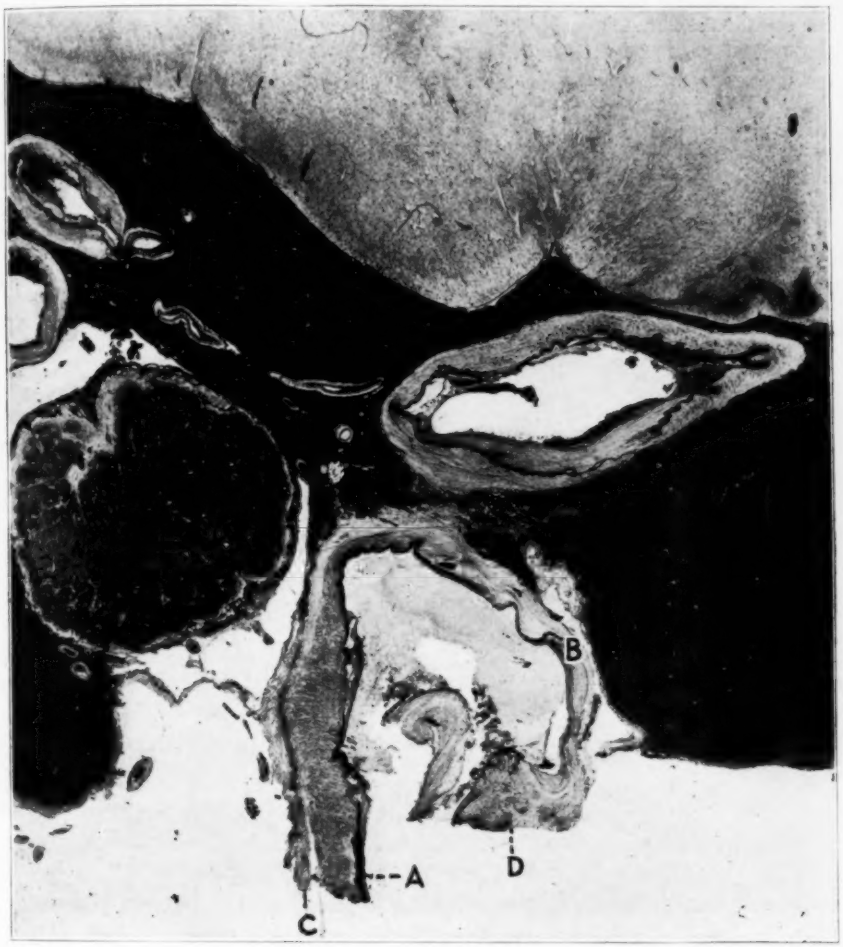


Fig. 8 (case 9).—Aneurysmal sac with the elastic tissue layer extending from *A* to *B*. The opened ends of the sac at *C* and *D* show the point of division which occurred when the brain was lifted from the base of the skull during removal. The antemortem point of rupture is shown in figure 9; × 10.

brain were made, and a small aneurysm was found in the internal carotid artery, which is shown in figure 6.

CASE 8.—*Initial fatal bleeding. Autopsy showed rupture of branch of posterior communicating artery without aneurysm formation.*

W. N., a medical student, aged 22, collapsed while exercising in the gymnasium. He was immediately admitted to the University of Virginia Hospital in a very serious condition, and died a few hours later.

Autopsy showed blood over the entire surface of the brain. Serial sections[3] through the circle of Willis showed a rupture of a branch of the left posterior communicating artery, as shown in figure 7.

CASE 9.—*Initial symptoms indicating a moderate amount of bleeding; gradual improvement until the twenty-first day; then severe bleeding followed by coma and hemiplegia; death forty-eight hours later. Autopsy showed a small ruptured aneurysm of the internal carotid artery.*

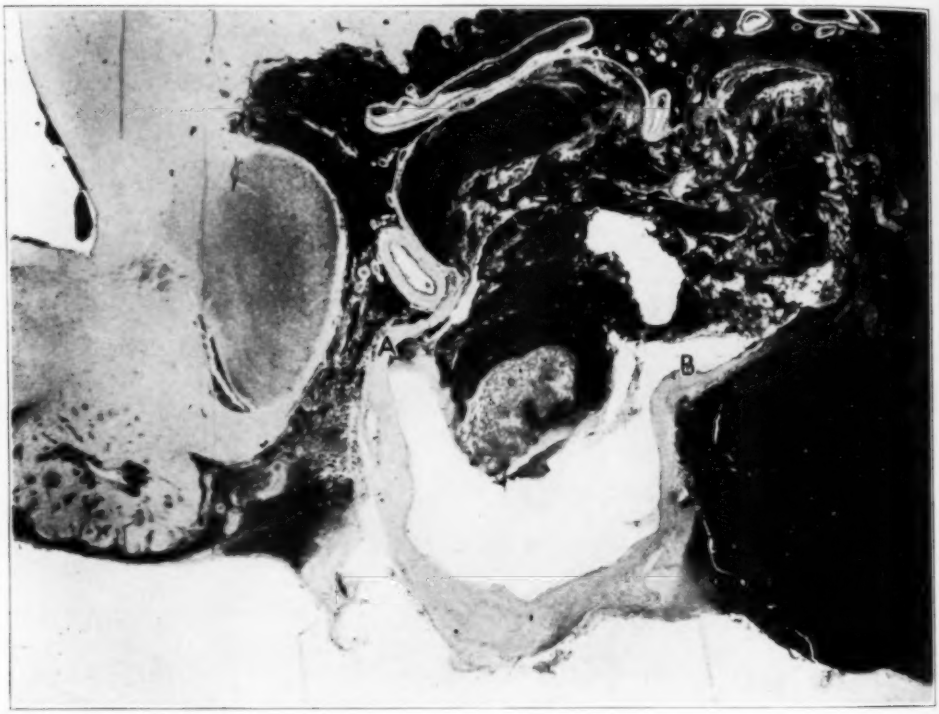


Fig. 9 (case 9).—The elastic tissue layer is entirely absent in the aneurysmal sac of the internal carotid artery, which has ruptured at *A* and *B*. Beyond this point there is a partially organized clot which marks the site of the initial bleeding. Beyond this is a more recent clot which occurred forty-eight hours before death. Reduced from × 10.

H. A. M., a single man, aged 47, had a sudden severe headache while digging to transplant a tree. The patient had a chill soon afterward, but there was no vomiting. The headache continued, and seven days after the onset he became delirious. On the following day he was admitted to the Maryland General Hospital.

3. Drs. Blackford, Lehman and Wilson, of the University of Virginia, provided the sections of this case, which Dr. Blackford is reporting in full in the Virginia Medical Monthly.

On admission, the patient was delirious; the temperature was 100 F. rectally; the blood pressure was 175 systolic and 75 diastolic; the respiratory rate was 20, and the pulse rate, 100; the leukocyte count was 13,300; the pupils were contracted, and there was a squint of the left eye which had been present from the age of 4 years. A roentgenogram showed some clouding of the maxillary antrums, and after these sinuses were washed out the patient gradually improved; it was thought that the meningeal symptoms were secondary to this condition. He was discharged from the hospital fourteen days after admission in what seemed to be a very satisfactory condition.

The headache persisted, and seven days later the patient was found in an unconscious state in his bedroom, lying across the bed with his bathrobe partly on, indicating that he had attempted to get out of bed and had fallen suddenly back. At this time I saw him in consultation with Dr. James F. Magraw and Dr. William G. Jack.

The patient was readmitted to the hospital in profound coma, with partial paralysis of the muscles of the right side of the body, including the face. Breathing was loud and stertorous; the blood pressure was 190 systolic and 80 diastolic; the pulse rate was 93; the respiratory rate was 18, and the temperature was elevated to 102 F. There was marked rigidity of the neck. The condition gradually grew worse. A diagnosis of a large cerebral hemorrhage was made; a lumbar puncture was not done, but the ventricle was tapped twenty-four hours after admission and a quantity of bloody cerebrospinal fluid was evacuated. The patient died forty-eight hours after admission.

Autopsy showed a large amount of blood at the base and extending over the cortex. During the removal of the brain the left carotid artery was found to be dilated just after entering the skull. Serial sections were made through this dilated left carotid artery, and from these the illustrations shown in figures 8 and 9 were taken. In figure 8 the dilated vessel is shown with a defect in the elastic tissue layer. In figure 9 the point of antemortem rupture of the sac is shown, while the remaining portion of the sac is entirely lacking in elastic tissue. The partially organized clot, just beyond the point of rupture, evidently marks the blood that had escaped at the time of the severe headache thirty-one days before death, and beyond this the very extensive recent bleeding is seen.

INTRACEREBRAL BLEEDING

GROUP 2.—TYPE C

Any part of the brain may become the seat of a cerebral hemorrhage. The central ganglia are the most common situations. Hemorrhage into the cortex of the cerebrum is much less common, and hemorrhages into the cerebellum are spoken of in the literature as rare. Intracerebral bleeding may be divided clinically into types C and D. This division is made with the view of making it possible, clinically, to select from a large group of cerebral apoplexies a relatively small number for surgical attack. The division is based primarily on the location of the lesion, which is deep in the substance of the brain in type C, and more superficial in type D. Clinically, the types can be differentiated by the neurologic observations and the progress of the symptoms.

In type C, paralysis is noted early and persists because of the anatomic interruption of the internal capsule fibers. The deep reflexes are usually abolished, and the limbs on the opposite side are motionless

and flaccid. In slight bleeding, when only a small amount of blood is extravasated, these symptoms may disappear and an operation become unnecessary. On the contrary, after a large hemorrhage the condition of the patient is serious, and surgical aid may be sought. In this stage there is likely to be marked disturbance of respiration, which is of the Cheyne-Stokes or stertorous type; the pulse rate is rapid, and the temperature is elevated, sometimes to a marked degree. The paralysis persists, and the reflexes do not return in the affected side.

This type of lesion is well known, and although many of these patients die, I think that surgery has little to offer because of the

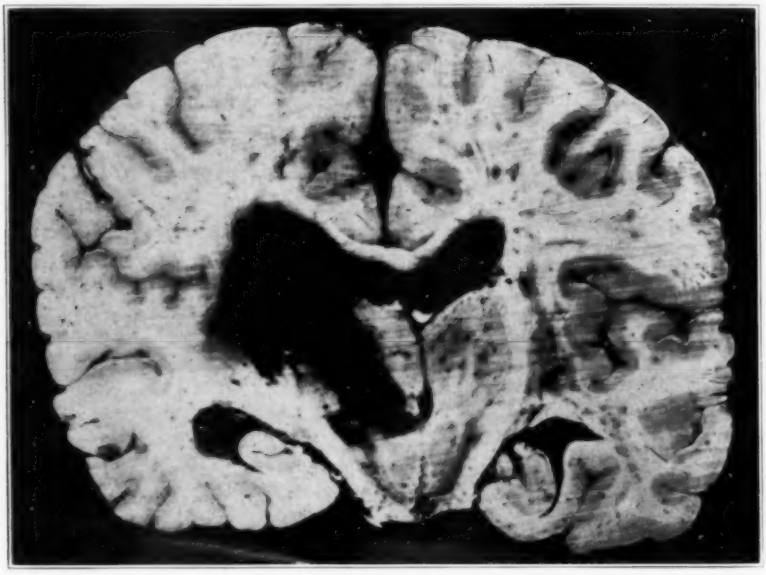


Fig. 10 (case 10).—A large hemorrhage in the right hemisphere. The extensive destruction of the deep structures and rupture of the ventricles render surgery useless.

serious damage to the brain and the inaccessibility of the lesion. For the purpose of differentiating this from type D, however, I shall include three cases. The ages of these patients were 27, 41 and 48 years.

REPORT OF CASES

CASE 10.—*Sudden complete loss of consciousness with hemiplegia in a relatively young woman who had had high blood pressure for five years; death on the fifth day. Autopsy showed a large hemorrhage which had ruptured into the ventricle.*

M. L. K., a single woman, aged 41, was seen in consultation with Dr. Walter W. White, Jr., and was admitted to the Union Memorial Hospital. The patient had been a semi-invalid for five years preceding the present illness because of high blood pressure, which had been ranging slightly above 200 mm. of mercury. The

present illness began suddenly without prodromal symptoms. The patient was found in her home, unconscious, with paralysis of the left side of the body. The stupor continued without improvement until death, five days later. The temperature during the last twenty-four hours gradually rose to 108 F.; the pulse rate was quick; the urine contained a large amount of albumin, and the fundi showed marked edema with numerous small hemorrhages. The rising temperature, rapid respiration and complete paralysis of the left side led to the conclusion that the lesion was deep seated and that nothing was to be accomplished by an operation.

Autopsy showed the surface of the brain to be normal. Sectioning after fixation showed a large hemorrhage in the right basal ganglia, which had ruptured into the ventricle, as shown in figure 10. There was also well marked chronic nephritis. An operation was contraindicated not only by the location of the hemorrhage in this case but by the previous history of the patient, which indicated serious

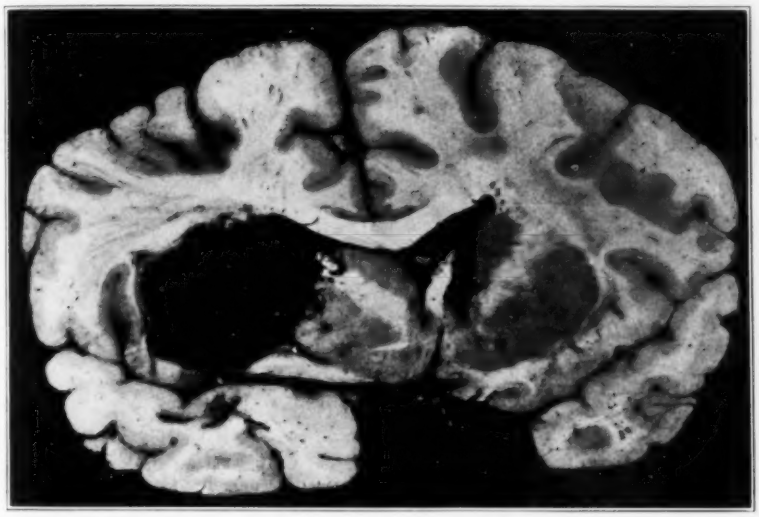


Fig. 11 (case 11).—A large hemorrhage occurring deep in the substance of the brain during labor in a patient, 27 years of age.

vascular changes, the cerebral hemorrhage merely marking the terminal stage of a general arteriosclerosis. This is often true in older people, in whom it is foolish to attempt to prolong life. This, however, does not justify the conclusion that all patients with cerebral hemorrhage are so badly broken physically that they should be allowed to die, as will be shown in some instances of recovery in cases of type D.

The following case seems worthy of note because of the early age at which a large fatal hemorrhage occurred during an obstetric delivery.

CASE 11.—*Extensive hemorrhage in the right hemisphere and brain stem during labor in a woman under 30; death in a few hours.*

L. S., a married woman, aged 27, entered the Bon Secours Hospital, in the service of Dr. Dudley Bowe, after a journey from her home in New York. Immediately after she entered the hospital, active labor began. The patient was anesthetized and delivery was accomplished without difficulty. The systolic blood

pressure before and during delivery varied from 136 to 152 mm. of mercury. The patient did not regain consciousness, but continued in a deep coma and died within a few hours.

A complete autopsy showed nothing abnormal in the chest or abdomen. The brain, however, showed a large blood clot in the right hemisphere (fig. 11). There were also multiple hemorrhages in the brain stem.

CASE 12.—*Occasional jacksonian seizures over period of twenty-two months; recent severe seizure followed by hemiplegia; exploration for a supposed tumor with bleeding; death. Autopsy showed large clot deep in the left hemisphere and arteriosclerosis.*

M. B. T., a married man, aged 48, was admitted to the Union Memorial Hospital in a state of collapse following a severe convulsion, and was seen with Dr. Samuel McLanahan. There was a history of jacksonian seizures for twenty-two months, which were followed by headache, weakness of the right side of the body

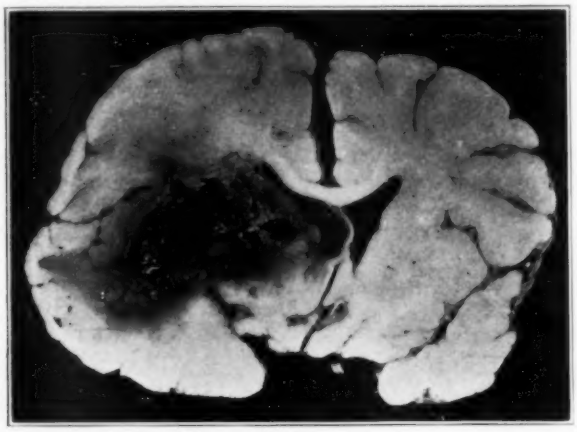


Fig. 12 (case 12).—A large hemorrhage in the left hemisphere secondary to cerebral arteriosclerosis. Jacksonian epilepsy for many months preceded the rupture.

and aphasia. The first occurred suddenly. The previous health had been excellent. These symptoms gradually cleared up, and he returned to work soon after the initial convulsion, but similar attacks occurred every few weeks, and he was obliged to give up work one year before admission to the hospital. During the last year, the intervals between attacks gradually became shorter, and the aphasia and right hemiplegia following the convulsions more marked. During this period headache had been troublesome.

When admitted he was in deep stupor, with complete right hemiplegia. Ophthalmoscopic examination showed slight tortuosity of the veins and blurring of the disk margins; the optic cup was filled. Because of the previous history of jacksonian attacks, associated with aphasia and right hemiparesis, the patient was thought to have a tumor, and it was concluded that there had been bleeding into the tumor prior to admission. The condition of the patient did not permit an operation at the time of admission and it was hoped that he would improve. The blood pressure on admission was 200 systolic and 130 diastolic. The patient gradually grew worse. Sixteen days after admission a left craniotomy was

done. The hemisphere was very tense, and a cannula introduced through the cortex showed only a large amount of blood and no evidence of tumor. Nothing further was done. The patient died on the following day.

Autopsy revealed a large blood clot in the left hemisphere, as shown in figure 12. The lesion had extended to the ventricular wall, but had not ruptured into the ventricle. The case is of interest in showing a long history of cerebral irritation, simulating tumor in an arteriosclerotic brain.

GROUP 2.—TYPE D

In type D I shall include cases that may be helped surgically. Surgical intervention is possible because of the superficial location of the clot, but the determination of the location of the clot is not always easy.

In this type the onset is acute, but the progress of symptoms is usually more gradual than in the other types described. The symptoms are largely those of increased intracranial pressure, without elevation of temperature, and they tend to become serious during the second week. Focal symptoms are present or absent depending on the location of the clot. Local pain commonly occurs. Hemianopsia is valuable in determining the presence of clots in the occipital and temporal lobes. The most valuable neurologic disturbance is that due to secondary pressure on the internal capsule when the lesion is in the frontal and temporal lobes, the latter being, in my experience, the most common site of these hemorrhages. The loss of muscular power may be only partial, and is likely to be greater in one or the other extremity. The deep reflexes may be retained or only slightly altered, and both the muscle power and the reflexes may vary from day to day. When there is evidence of a marked increase of intracranial pressure with only partial disturbance of the musculature, one can say that the clot is not likely to be in the internal capsule.

The surgical consideration of these cases must take into account the possibility of spontaneous cure and the poor surgical risk of patients with a general cardiovascular condition. Simplicity of procedure is necessary, and in the majority of cases possible, because of the process of liquefaction and the formation of a cyst. In the beginning the focus of bleeding is a solid mass; if it is to be removed at this time it must be attacked through a craniotomy with its consequent strain on the patient. The early complete removal of the clot may be followed by further bleeding. On the other hand, a delay of a few days will allow time for an indication of spontaneous recovery or the beginning of cyst formation. An example of spontaneous recovery after a hemorrhage of moderate size in the temporal lobe is shown in figure 14. This lesion was found during the examination of the brain in case 18, in which the patient died following a large cerebellar hemorrhage, shown in figure 16. One year prior to death, the patient suddenly complained

of headache and nausea and was forced to remain in bed for one week, after which he resumed work but complained of vague symptoms. A diagnosis of a nervous breakdown was made, and the patient was advised to lighten his work. When the brain was cut, after fixation in formaldehyde, the cavity contained several cubic centimeters of a thin dark brown fluid surrounded by a firm wall. A photomicrograph is shown in figure 15. The innermost layer contains many pigment-loaded cells, and the outer portion is made up of proliferated neuroglia elements. This lesion is a good example of an apoplectic cyst. The development of a cyst may be likened to the formation of an abscess in the brain, whereby a diffuse lesion becomes circumscribed and capable of evacuation.

The process of liquefaction and cyst formation is dependent on whether the bleeding occurs at one time or continues over a period of days. In the latter type of bleeding the prognosis is more grave, regardless of the time of surgical attack. On the other hand, when there is an immediate outpouring of blood, with little or no subsequent oozing, the formation of a cyst through liquefaction of the clot and organization of the surrounding nerve elements begins within the first few days.

Complete evacuation of the extravasated blood can perhaps not be accomplished through one aspiration, but a recent experience (case 16) suggests the advisability of repeating the procedure until there is no further evidence of the cyst. In this case a needle was introduced through the original trephine opening and 19 cc. of yellowish-brown fluid was removed from the temporal lobe, five and one half months after the original evacuation. In the light of this finding an earlier second aspiration would have been advisable. Repeated aspiration, therefore, seems to me the operation of choice.

In one patient (case 17) I failed to find the focus of bleeding, and the condition of the patient, though serious at the time, gradually improved after a subtemporal decompression. The early uncovering and complete removal of a hemorrhage through an osteoplastic flap may become the operation of choice in patients physically able to stand the procedure and in whom a delay seems dangerous because of the serious degree of increased intracranial pressure.

REPORT OF CASES

CASE 13.—*Sudden onset, with gradually increasing symptoms; hemiparesis; partial evacuation of a clot in the left temporal lobe; death ten days later. Autopsy showed a clot in the left temporal lobe and bilateral lobar pneumonia.*

G. M., a married woman, aged 39, while riding in an automobile suddenly complained of headache in the frontal region. She returned home and could walk with assistance. Five hours later, she complained of dim vision. On the following day she was entirely disoriented and was admitted to the Mercy Hospital to the

service of Dr. Maurice C. Pincoffs. At the time of admission she was in coma; the blood pressure was 220 systolic and 110 diastolic. There was rigidity of the neck, and the Kernig sign was suggestive. The muscles of the right upper and lower extremities showed diminished power, but were not entirely paralyzed. There was a positive Babinski sign on the right, but this was absent on the left. Ophthalmoscopic examination showed edema of the disks and dilatation of the retinal veins. Twenty-four hours after admission, the patient was slightly more rational, with a systolic blood pressure of 240.

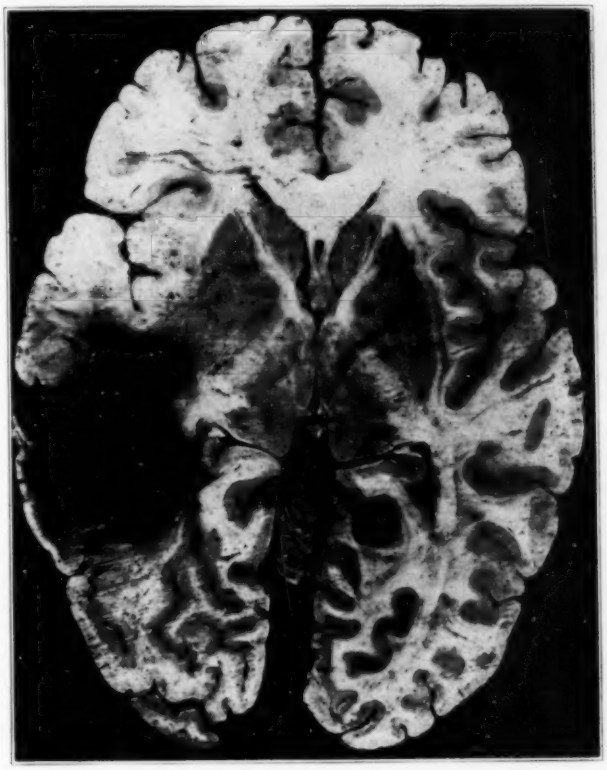


Fig. 13 (case 13).—A hemorrhagic focus in the left temporal lobe. Note the superficial location of the clot, with the basal ganglia entirely uninvolved. This lesion was diagnosed clinically and was partially evacuated with relief from the symptoms of increased intracranial pressure. Note the absence of the distortion of the brain. The patient died of lobar pneumonia ten days after operation.

Four days after admission, she was in deep coma and the condition looked very unfavorable. Through a small left subtemporal decompression the temporal lobe was exposed and found to be blood stained. Immediately beneath the cortex there was a blood clot which was fairly firm, but the cavity contained a moderate amount of liquid blood which was easily removed. There was a definite increase of intracranial tension, which was reduced after the removal of the blood. The entire clot was not removed, as this was not necessary to diminish the intracranial tension

to a normal degree and there was fear of exciting additional bleeding. Following the operation there was improvement for several days. The blood pressure was 160 systolic and 110 diastolic. Two days later, it was 200 systolic and 140 diastolic.

Six days after the operation, there was a troublesome cough and other evidence of pneumonia. From this time on, pulmonary symptoms progressed, and the patient died ten days after the operation. There was no bulging at the site of the decompression, so that further evacuation of the cyst was not indicated.

Autopsy showed definite lobar pneumonia. There were complete consolidation of the lower lobe of the right lung and partial consolidation of the lower lobe of the left lung. The kidneys were small and contracted. The brain showed the hemorrhage in the left temporal lobe seen in figure 13. The blood was well circumscribed and was limited to the cortex, the basal ganglia and internal capsule being entirely free. The paralysis of the right side of the body was due to edema rather than to interruption of the motor tract fibers. The brain was not distorted, so that it seems unlikely that death was due to increased intracranial pressure.

The following case is included because of the gradual onset of the symptoms suggesting the possibility of a tumor. The patient had been having severe headaches for two months. At the time of admission there was some bleeding, but severe bleeding did not take place until seventeen days later. This was followed by serious symptoms, and an operation was undertaken after three days. The extravasated blood was encountered, but was not liquefied sufficiently to flow through a cannula, a point, I think, of definite clinical importance, as will be shown in case 16 in which the blood was liquefied two weeks after the onset of the symptoms and was easily evacuated.

CASE 14.—*Gradual onset of symptoms during six months; severe headache five days before admission; cerebrospinal fluid slightly xanthochromic on admission; seventeen days later, a sudden increase of intracranial pressure and weakness of the muscles of the right side of the body; exploration for supposed tumor with bleeding; recent blood clot found; death twenty-four hours later. Autopsy revealed a large blood clot in temporal lobe and basal ganglia.*

J. B., a colored man, aged 49, whose past history included measles and mumps in childhood and pneumonia at the age of 39 years, at the age of 23 had gonorrhea with a definite sore, for which he received treatment in a dispensary; no further history of syphilis was obtained. Four years before the present illness he had been treated in a dispensary for cardiovascular disease. The Wassermann reaction of the blood was then negative. Six months before the onset of the present trouble, the patient had shown personality changes, with definite loss of memory. About one month before admission, he had headache with occasional attacks of nausea and vomiting, associated with mental confusion and loss of memory. Five days before entering the hospital, he had a severe fronto-occipital headache, of the dull boring type, which was constant.

When admitted to the Baltimore City Hospital, to the service of Dr. Thomas R. Boggs, he complained of headache and was stuporous. The urine contained albumin; the blood pressure was 210 systolic and 55 diastolic. Ophthalmoscopic examination showed no evidence of increased pressure. The deep reflexes were hyperactive, and there was no evidence of muscular weakness in any group. The Wassermann reactions of the blood and cerebrospinal fluid were negative. The spinal

fluid was slightly xanthochromic. Three days later, the patient was much improved and rational, and the headache had disappeared. On the thirteenth day in the hospital, a second lumbar puncture was done, and the fluid was less colored. On the seventeenth day, there was a sudden change in the condition. The patient complained of headache and vomited. On the following day he was stuporous. When aroused he complained of headache over the frontal region. There was a right hemiparesis, which was more marked in the arm than in the leg. The reflexes were hyperactive and the Babinski sign was positive on the right. Forty-eight hours later, the paralysis of the right arm and leg gradually increased, but was never complete and was less marked in the leg than the arm. The stupor progressed and the condition became critical.

The left hemisphere was explored, three days later, through a small decompression, and a cannula introduced into the cortex encountered old blood which, however, was too thick to be evacuated through the needle. The cortex was incised with a view to eliminating the possibility of a tumor, but none was found and no attempt was made to remove the clot encountered at some depth below the surface. The patient died twenty-four hours later.

Autopsy showed a large blood clot, located chiefly in the temporal lobe; mesially it had destroyed the external capsule fibers and the lateral portion of the basal ganglia. The hemorrhage was large, and there was marked distortion of the brain.

CASE 15.—*Sudden onset of symptoms; improvement until eighth day; sudden change; on tenth day condition serious, with complete coma, paralysis of right arm and face and weakness of right leg; aspiration of 30 cc. of old blood from lower motor area and subtemporal decompression; gradual but complete recovery.*

W. H. T., a married man, aged 43, whose past history was unimportant except that for six months prior to the sudden onset of the present illness he had been very emotional and apprehensive, had taken his work as a foreman in a shipyard very seriously. He said that on one or two occasions he had been treated badly by his associates and that in one of these upsets he had cried bitterly. During this period he had occasional slight headaches. At 5 a. m. he was awakened by a very severe headache and told his wife that something was wrong. This was followed by slight mental confusion. Three days after the onset, I saw him in consultation with Dr. J. Kennedy Corse at the Newport News Hospital. The patient was dull, but could be aroused; the pulse rate was slow; the left pupil did not react to light; the Babinski sign was positive on the right; there was slight aphasia; there were no muscle twitchings or convulsive seizures. There was slight edema of the disks. The Wassermann reaction of the blood was negative.

The condition improved, and six days after the beginning he answered questions well and the headache was less severe. Eight days after the onset there was a sudden change in the condition; he became more stuporous, and there was partial paralysis of the right arm. Forty-eight hours later, I again saw him. He was in a deep stupor, with paralysis of the right arm and face and some weakness of the right leg. The pulse and respiratory rates were increased, the temperature was elevated and the blood pressure was 120 systolic and 100 diastolic. Examination of the lungs did not show signs of pneumonia, but the general appearance of the patient suggested that there were pulmonary changes, as his face was flushed, he was perspiring profusely and he could not be roused. At this time the patient was removed to the operating room and a trephine opening was made over the lower motor area. A needle was introduced to a distance of 4 cm. below the surface, and about 30 cc. of dark liquid blood flowed gently through the needle. This entirely relieved the tension, but because of the serious condition of the patient a right subtemporal decompression was done and he returned to his room improved.

Forty-eight hours after the operation, the patient moved the right arm. After he regained consciousness it was evident that he was aphasic and had a complete right homonymous hemianopia. The aphasia slowly improved and entirely disappeared, but when the patient was examined a year later there was a marked homonymous defect in the visual fields. The patient returned to his duties six months after the operation; it is now almost eight years, and he has had no recurrence of the trouble. He has been promoted and his duties are heavier than before.

This was the first case of this type that had come under my observation and the finding of the blood was largely accidental. The cannula was introduced into the lower motor area because only the right arm was paralyzed. The outcome was good, no doubt because the period of time that elapsed between the bleeding and the operation allowed the necessary interval for the blood to become liquid.

CASE 16.—*Sudden loss of consciousness with partial hemiplegia; gradual progress of symptoms; on twelfth day, complete hemiplegia and deep stupor; aspiration of 40 cc. of old blood from the temporal lobe; gradual improvement of symptoms; five and a half months later, residual paralysis and some aphasia; aspiration of brownish-yellow fluid from temporal lobe cyst.*

C. S., a married man, aged 35, a quarry foreman, became greatly overheated on a hot day in July, complained of severe headache, and one hour after the onset of the symptoms was found unconscious, with partial paralysis of the right side of the body. Occasionally, during the previous five months, he had complained of shortness of breath and had had some headache, but had not seen a physician except for an examination of his eyes during the year preceding.

Ten days after the onset of the illness, I saw the patient at his home in consultation with Dr. Albert L. Wilkinson. At this time he was completely paralyzed on the right side and there was gradually increasing stupor. Admission to the hospital with a view to evacuating the blood was recommended if he did not improve. During the following forty-eight hours the stupor increased, the condition seemed less favorable and the patient was admitted to the Union Memorial Hospital on the twelfth day after the onset of the illness. At this time he was in a stupor but could be roused slightly. The blood pressure was 160 systolic and 120 diastolic. The pupils were equal and reacted to light and in accommodation. Ophthalmoscopic examination showed well marked edema, with slight elevation of the disks. The right arm and leg were motionless, and the patient was completely aphasic. The deep reflexes on the paralyzed side were present and slightly exaggerated. There was a positive Babinski sign on the paralyzed side but a negative sign on the left. The temperature ranged from 98 to 99.3 F., and the pulse rate was between 70 and 80. The leukocyte count was 10,400 and the Wassermann reaction of the blood was negative. The specific gravity of the urine was 1.018, and there was a trace of albumin. The nonprotein nitrogen was 53.4 mg. per hundred cubic centimeters of blood, and the blood sugar was 121 mg. per hundred cubic centimeters.

On the following day, the patient was a little more responsive, the condition being otherwise unchanged. Forty-eight hours after admission, when the condition seemed very unfavorable, a needle was introduced into the temporal lobe through a small opening in the left temporal region, and 40 cc. of thick tarlike blood was evacuated. Forty-eight hours after the operation, the patient was more alert. The blood pressure was 156 systolic and 115 diastolic. Five days after the operation, the patient mumbled such things as "good-bye," and from this time his speech improved steadily so that he was easily understood. He was very emotional and cried a great deal. Eight days after the operation there was a slight movement of the fingers of the paralyzed hand. The patient was discharged from the hospital

nineteen days after the operation, talking fairly well, with satisfactory motion of the lower extremity and some movement of the upper extremity. At this time the nonprotein nitrogen was 33.9 mg. per hundred cubic centimeters of blood. Two months after the operation, the patient was able to walk very well, and talked with some hesitation but quite satisfactorily. The right upper extremity was still very weak, but there was movement in all the muscle groups. The systolic blood pressure was 140 mm. of mercury.

Four and one-half months after the operation, there was still a marked weakness of the muscles of the right upper extremity, with less weakness of the muscles of the right lower extremity, and the patient was still somewhat aphasic. At this time he had a general convulsive seizure lasting about three minutes. For several days following the attack the patient was more awkward in using the right arm and leg, and the blood pressure was 146 systolic and 118 diastolic. Each morning for a week after the convulsion he was nauseated and occasionally complained of headache.

About three weeks after the convulsive seizure, when the patient was making poor progress, he was readmitted to the hospital for further study. The blood pressure at this time was 152 systolic and 110 diastolic; the urine contained a trace of albumin, and the phthalein test showed: first hour, 50 per cent; second hour, 10 per cent. The nonprotein nitrogen on the day of admission was 42.8 mg. per hundred cubic centimeters of blood, and the blood sugar was 128 mg. On the following day the nonprotein nitrogen was 28 mg. and the blood sugar was 85 mg. per hundred cubic centimeters. On the third day, the nonprotein nitrogen was 30.7 mg. and the blood sugar was 81.6 mg. per hundred cubic centimeters.

A lumbar puncture needle was introduced through the original trephine opening in the left temporal bone to a depth of 5 cm. from the level of the scalp; a syringe was attached, and 19 cc. of thin yellowish-brown fluid was evacuated. The fluid was apparently not under pressure, as it did not flow through the needle, and the aspiration with a 2 cc. syringe was done very slowly until the cavity was completely empty. The procedure was a simple one, and the patient was discharged on the same day. Immediately after the evacuation the patient stated that his head seemed clearer, and during the following twelve hours there was improvement in speech.

When the patient was examined a week later, the condition of the arm and leg showed definite improvement. The possibility of the cyst refilling will be determined by another aspiration after an interval of one month.

CASE 17.—*Sudden headache with hemiparesis; gradual progress of symptoms; on the nineteenth day, almost complete hemiplegia and stupor; right subtemporal decompression; complete recovery.*

D. R. T., a married man, aged 34, while at dinner had a sudden pain in the head and, about three hours later, the left upper and lower extremities became weak. He was admitted to the Union Memorial Hospital three days later, and was seen in consultation with Dr. Harry Tull. He complained of severe headache; the blood pressure was 124 systolic and 76 diastolic, and there was definite weakness of the entire left side of the body. The patient remained in the hospital for one day and then went home, where he was seen fourteen days later in the Peninsular General Hospital at Salisbury, Md. At the time of this examination the condition was grave. There was a fairly complete left hemiplegia; the temperature was 100.5 F. and the patient was stuporous. A right subtemporal decompression was done and the cannula passed into the lower motor area, but no lesion was found. It was noted that there was an increase of intracranial pressure, and a decompression was done.

Recent experiences have led me to believe that this patient had a clot in the temporal lobe, and I think it likely that the blood would have been found if attention had been directed to this instead of to the parietal lobe. It is interesting to note that in spite of the fact that the blood was not evacuated the patient slowly improved and returned to light duty within several weeks. There has been no recurrence of the symptoms during the two year interval, and the patient is carrying on his full duties.

The two following cases are cited as examples of large circumscribed hemorrhages that should have been attacked surgically. In one of them, case 19, the diagnosis was not made and the patient died with rapidly progressing signs and symptoms of a medullary disturbance believed to be of an inflammatory type.

In the other, case 18, which came under observation shortly after the experience in case 19, the symptoms were recognized and operation was determined on. In the belief that the patient was improving, however, the procedure was delayed until twenty-four hours before death, when the symptoms suddenly became very grave, and the patient was removed to the hospital for an operation. On arrival the condition was too grave to permit intervention.

CASE 18.—*Sudden onset of symptoms suggesting a lesion of the posterior fossa; death after two weeks. Autopsy showed a large recent clot in cerebellar hemisphere and an apoplectic cyst in temporal lobe.*

E. O. W., a married man, aged 58, after a very active day and immediately after dinner, suddenly complained of a severe pain in the occipital region, followed by a general headache. Within a few hours he was delirious and continued in this state for about one week. At this time I saw him in consultation with Dr. Charles R. Foutz and Dr. Henry M. Fitzhugh. There was some uncertainty of the muscles of the left upper and lower extremities. The confused mental condition made it difficult to determine whether this was partial paralysis or incoordination. Vomiting was troublesome and there was well marked nystagmus. A lumbar puncture showed blood-stained cerebrospinal fluid. The symptoms gradually progressed, and during the latter part of the second week the patient had three attacks marked by a sharp rise in the respiratory and pulse rate. It was concluded that these attacks were due to medullary pressure, secondary to hemorrhage in the cerebellum, and the patient was removed to the hospital for operation. On arrival, however, the condition was too serious, and the patient died eighteen hours after admission.

One year prior to this attack, he had had a somewhat similar illness with a sudden onset and severe headache. The diagnosis of a nervous breakdown was made, and the patient remained off duty for some days, but the headache continued for several weeks. This history was interesting in the light of the autopsy observations, which showed, in addition to the recent lesion, which was a large hemorrhage in the left hemisphere of the cerebellum (fig. 16), an old blood cyst in the right temporal lobe (fig. 14). The wall of this cyst contained a large number of pigment cells, as shown in figure 15.

CASE 19.—*Gradual onset of symptoms with final severe increase of intracranial pressure and death. Autopsy showed large cerebellar hemorrhage resulting from bleeding in angiomatous area.*

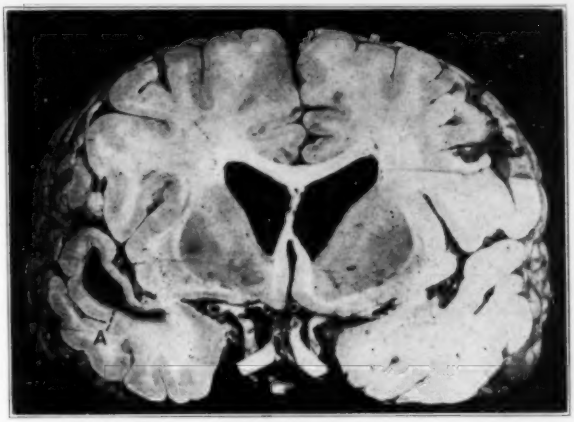


Fig. 14 (case 18).—The cavity in the right temporal lobe at *A* is an apoplectic cyst believed to be the result of a hemorrhage in this area one year prior to death.

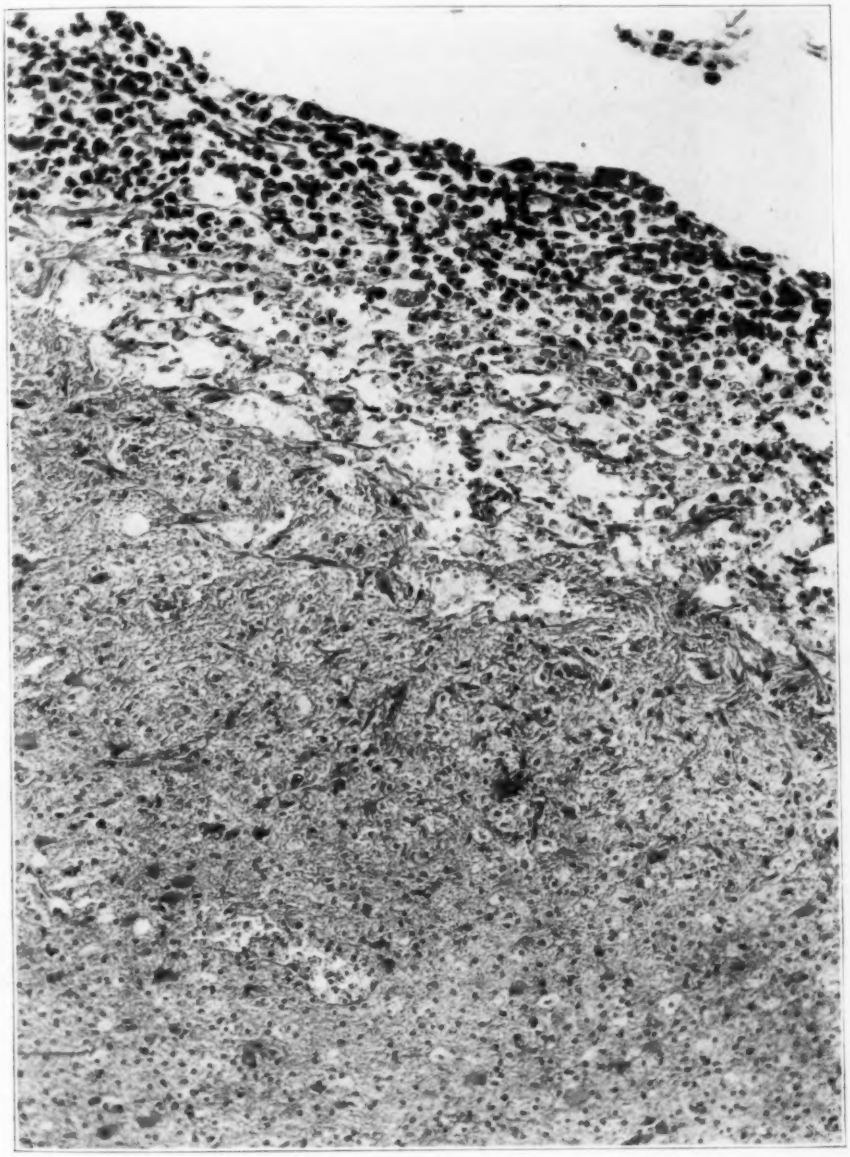


Fig. 15 (case 18).—A section of the wall of the cyst shown at *A* in figure 14. The inner layer of the wall contains a large number of pigment-loaded cells, while the outer portion shows marked proliferation of the neuroglia and fibrous tissue elements; × 125.

W. C. A., a boy, aged 14, was admitted to the hospital five days after a boxing bout with a playmate, which was followed in twelve hours by some headache. During the bout there had been no injury to the head and the child felt no ill effects following the exercise, except that he was much overheated. On the following morning, however, there were suboccipital pain and stiffness of the neck, later associated with vomiting, dizziness and general headache. The symptoms gradually progressed and five days after the onset the patient was admitted to the Union Memorial Hospital and seen in consultation with Dr. Sydney R. Miller.

On physical examination there was pronounced nystagmus to the right and slight nystagmus to the left. The finger-to-nose test was well performed on both sides. The cerebrospinal fluid was clear, with 13 cells per cubic millimeter. The pulse was rather slow, and there was diplopia. Four days after admission, the headache was more severe, and there was stupor from which the patient roused every few minutes and complained of severe headache. Twenty-four hours before

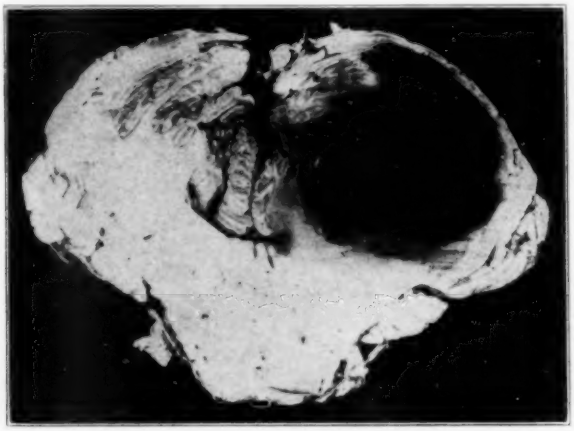


Fig. 16 (case 18).—A large hemorrhage in the cerebellar hemisphere which occurred two weeks before death and produced symptoms indicating cerebellar involvement. This lesion was diagnosed clinically, but operation was delayed with the hope of recovery until the condition of the patient was too serious to permit evacuation.

death there was no choking of the disks, but slight enlargement of the retinal veins. Nystagmus disappeared. The left pupil was smaller than the right. The patient was in coma, and death resulted twelve days after the onset of the symptoms.

Autopsy showed a large cavity filled with blood in the right cerebellar hemisphere, as shown in figure 17. The clot occupied practically the entire hemisphere, with only a thin margin over the cortex on the posterior surface. There was staining of the surface, and a lumbar puncture toward the latter part of the course would perhaps have shown blood-stained cerebrospinal fluid. As the fluid was clear in the beginning, the clot was in all probability small and did not reach the surface of the cortex, as shown in the figure.

After fixation in formaldehyde the blood clot was carefully removed so that the wall of the cavity could be examined. At one point there was a shred of tissue, in contrast to the remainder of the wall which was smooth. A block was removed from this site and sectioned serially. The sections showed a collection of blood

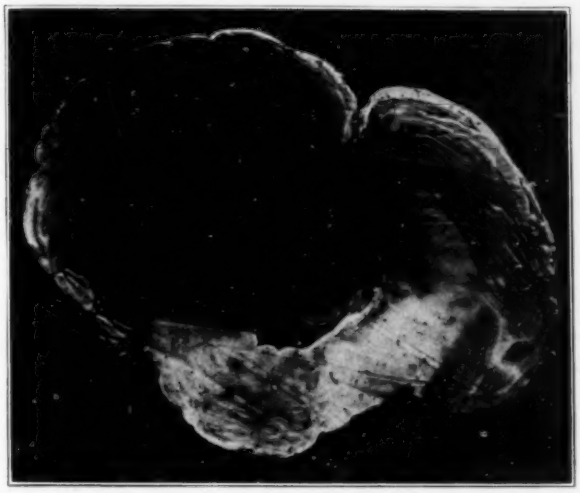


Fig. 17 (case 19).—A large cerebellar hemorrhage which produced symptoms over a period of several days and was not diagnosed, but could perhaps have been removed.

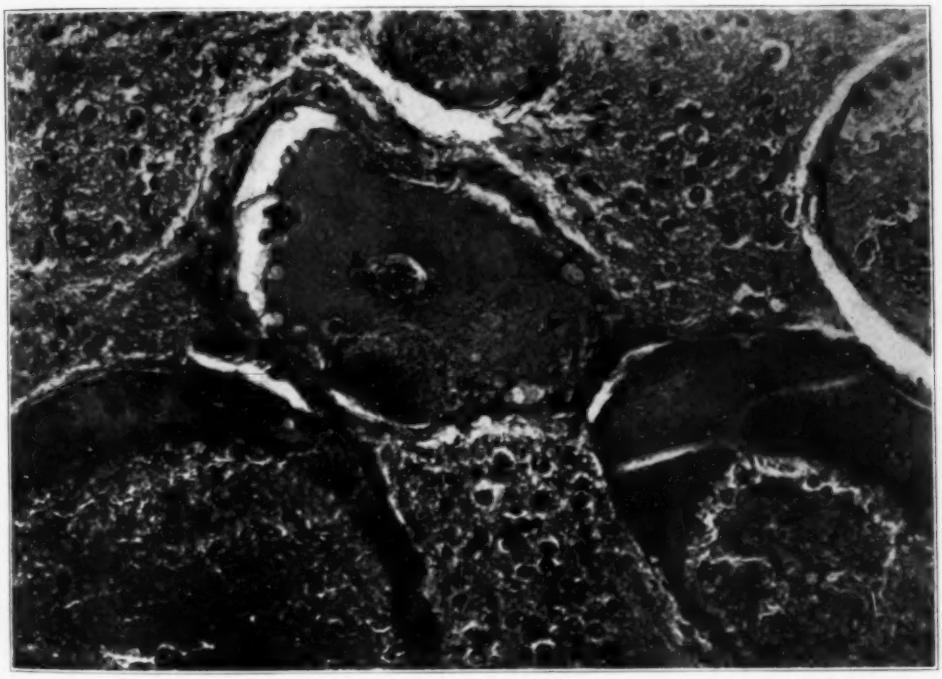


Fig. 18 (case 19).—Portion of the cerebellum surrounding the blood clot shown in figure 17, with numerous vessels. This is a part of a small angioma in this region which was the cause of the bleeding. Reduced from × 500.

vessels as shown in figure 18. The diagnosis of an angioma was made, and it is probable that some of these thin-walled vessels ruptured during the strain of boxing and the extravasated blood caused other vessels of the lesion to give way, resulting in a slowly increasing clot.

The lesions found post mortem in cases 18 and 19, as shown in the illustrations (figs. 14 to 18), because of their circumscribed character definitely indicate the surgical possibilities of such conditions even more convincingly than does the clinical course in the cases of operation and recovery in which it is impossible to demonstrate the actual lesion.

COMMENT

Spontaneous meningeal bleeding is frequently secondary to aneurysms of the larger and medium-sized vessels at the base, to a direct rupture of a congenitally weak artery, a type carefully studied by Dr. Wiley D. Forbus,[4] or to vessels damaged by arteriosclerosis, syphilis, bacterial infection or trauma. This report includes seven fatal cases of meningeal bleeding. In all of the cases the hemorrhage occurred at the base of the brain.

The ruptured vessel was found in each case in the serial sections, which according to our routine include the circle of Willis and its branches for a short distance. In no case was more than one aneurysm found. The arteriosclerotic type of alteration was found in cases 3, 4, 6, 7 and 9. The ages of these patients were 40, 51, 60, 41 and 47 years. In five of the cases, ruptured aneurysms were found; in cases 4, 5 and 6, aneurysms of the anterior cerebral artery; in cases 7 and 9, aneurysms of the internal carotid artery. In case 3 there seems to have been a rupture of an arteriosclerotic vessel (fig. 1) without the formation of an aneurysm. The same type of lesion was found in case 8 (fig. 7). The changes in the vessel wall consisted chiefly in the lack of elastic tissue of the vessel that ruptured. The vessel was a branch of the posterior communicating artery, which is also shown at *A* in figure 7. This, like other arteries of this brain which were examined both at the base and over the cortex, shows no evidences of arteriosclerotic changes. The appearance of the vessel in this case indicates that the bleeding resulted from a bursting of the wall without aneurysmal formation. The age of the patient and the lack of arteriosclerotic changes in this and other vessels would indicate that this was a congenitally weak vessel which gave way under moderate strain.

In case 1 of this group the patient had been having arthritis and evidences of infected teeth and tonsils, and did not present signs or symptoms of vascular disease, so that it seems fair to suppose that the bleeding was the result of infection or inflammatory change in the vessel wall.

---

4. Forbus, Wiley D.: On the Origin of Miliary Aneurysm of the Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. **47**:239 (Nov.) 1930.

In case 5 the possibility of an infection seems even more likely in that the patient had recently gone through a long period of disability because of extensive burns of the body surface. The burns in this case required the patient to remain in the hospital for four months, and the history stated that he suffered from "nervousness." After his discharge from the hospital the patient suffered from insomnia and was restless and irritable, these symptoms indicating a cerebral circulatory disturbance during the period prior to the sudden rupture of the vessel.

In case 2 the bleeding probably originated in a small aneurysm secondary to vascular changes. The patient was definitely of the apoplectic type, much overweight, of florid complexion and nervous temperament, working long hours and intemperate in his habits of eating and drinking. The probability of an aneurysm was further indicated by the presence of a slight bruit in the right temporal region.

In a previous report,[5] the specimens from four proved cases of aneurysms of the anterior cerebral artery were studied. The youngest patient in this series was 12 years of age, and the ruptured aneurysmal sac was the only diseased vessel found. I think that this case should be put down as an aneurysm due to congenital defect. In another case, a man, aged 42, gave a history which suggested cerebral bleeding at the age of 22 years, and a large calcification was found in the region of the anterior cerebral artery which I concluded was the result of the previous bleeding. In this man there were three episodes of bleeding, and the examination suggested that they occurred in the same neighborhood. The early age at which this bleeding occurred and the fact that the lesions were multiple led to the belief that they were of the type that Dr. Wiley D. Forbus described as multiple miliary aneurysms due to congenital defects in the muscularis. In the other two cases in the report the patients were 41 and 37 years of age. No other aneurysms were found, but the other vessels showed definite arteriosclerotic changes and these aneurysms can therefore best be classified as secondary to arteriosclerosis. In the fifth case in this report a diagnosis of ruptured anterior cerebral aneurysm was made on the clinical findings. The patient was 34 years of age and recovered. There was no evidence of arteriosclerotic changes, and it was concluded that the lesion was due to a congenital vascular defect. It is now five years since the illness, and the patient has had no recurrence of the bleeding.

Syphilis is generally supposed to play a part in cerebral bleeding in the relatively young, but it seems to have been unimportant as a causative factor in my cases. In the five cases reported in 1928, the Wassermann reaction was negative in four, and because of the sudden death was not obtained in the fifth case. In this case, however, there was no history of syphilis. The Wassermann reaction was also negative in four of the cases of the meningeal type of bleeding of this report; in the remaining five it was not obtained because of the short duration

5. Bagley, C., Jr.: Blood in the Cerebrospinal Fluid: Resultant Functional and Organic Alterations in the Central Nervous System, Arch. Surg. **17**:18 (July) 1928.

of the illness. The impression that cerebral hemorrhage of the third and fourth decade of life resulted from syphilis antedates the period of accurate serologic study and is, I think, erroneous.

Under the heading of group 2, type C, three cases are cited for the purpose of showing the type of lesion in which surgery promises nothing. Two of the cases, 10 and 12, in patients aged 41 and 48 years, showed well marked arteriosclerosis and symptoms extending over many months. Case 12 has been included as an example of difficulty in diagnosis between hemorrhage and tumor. The sudden onset of symptoms indicating intracerebral bleeding in a patient with focal symptoms over a number of months will always offer some difficulty, as spontaneous hemorrhage in cerebral neoplasms is fairly common. The third case of this type occurred in the course of delivery. The patient was 27 years of age. In this case the Wassermann reaction was not obtained, as she entered the hospital during active labor, and died soon after. The Wassermann test was negative in the other two.

The etiologic factor in intracerebral bleeding has been the subject of discussion for many years, but particularly since the report of a ruptured miliary aneurysm in a woman, 43 years of age, by Gull [6] in 1859.

Charcôt and Bouchard,[7] in 1868, reviewed seventy-seven cases of spontaneous cerebral hemorrhage, and concluded that "miliary aneurysms" were the cause of the bleeding in every case. Other writers did not agree with Charcôt and Bouchard, and von Monakow,[8] in 1905, concluded that "miliary aneurysms" serve as the most important cause of hemorrhages but raised the question as to other possible causes such as atheroma and hyaline degeneration.

Ellis,[9] in 1909, studied twenty-six cases and concluded that the lesion responsible for spontaneous cerebral hemorrhage is arteriosclerosis, which apparently begins in the elastic layer and may involve all coats and result in simple rupture; or an aneurysm may form and be the seat of the bleeding.

Westphal [10] believed that in some cases the actual hemorrhage was preceded by a period of ischemia, the result of an angiospasm. During the period of the spasm the tissues surrounding the vessels were

6. Gull, William: Aneurysm of Cerebral Vessels, Guy's Hosp. Rep. **5**:281, 1859.

7. Charcôt, J. M., and Bouchard, C.: Nouvelles recherches sur la pathologie de l'hémorrhagie cérébrale, Arch. de physiol. norm. et path. **1**:110, 1868.

8. von Monakow: Gehirnpathologie, Vienna, Alfred Hölder, 1905.

9. Ellis, A. G.: The Pathogenesis of Spontaneous Cerebral Hemorrhage, Proc. Path. Soc., Philadelphia **12**:197, 1909.

10. Westphal, K.: Ueber die Enststehung des Schlaganfalls, Deutsches Arch. f. klin. Med. **151**:1, 1926.

altered, and after the return of the blood into the vessels this tissue did not offer sufficient resistance to the vessel wall and leakage occurred. This theory has not been generally accepted, but I believe it is the causative factor in some cases.

The excellent paper of Globus and Strauss [11] presents clinical and pathologic data which indicate that cerebral apoplexy is a final event and that it is preceded by softening.

The following case presented symptoms indicating severe cerebral circulatory upset, and the postmortem findings, as shown in case 20 (figs. 19, 20 and 21), I think illustrate the processes described by Westphal and

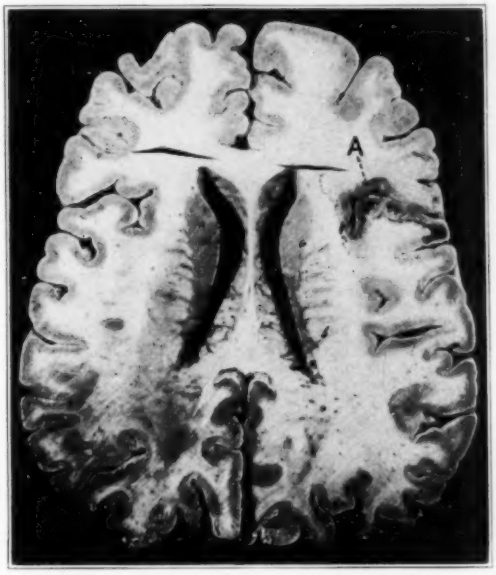


Fig. 19 (case 20).—Discolored cortex at *A*, corresponding to a soft area thought to have been the result of an angiospasm.

Globus and Strauss. This patient succumbed to pneumonia and a probable massive hemorrhage did not occur; thus a good opportunity for the study of the softened area was afforded.

CASE 20.—*Sudden serious mental upset with gradually failing cardiac condition; death eighteen days after onset. Autopsy revealed localized softening in left hemisphere with serious alterations of the small blood vessels and surrounding nerve tissue, and one small focus of bleeding.*

E. R., a single woman, aged 75, was referred by Dr. Armfield F. Van Bibber and admitted to the Church Home and Infirmary where she was seen in consulta-

11. Globus, J. H., and Strauss, I.: Massive Cerebral Hemorrhage: Its Relation to Preexisting Cerebral Softening, Arch. Neurol. & Psychiat. **18**:215 (Aug.) 1927.

tion with Dr. Oskar Diethelm. In spite of her 75 years, she had been actively engaged in teaching in a private school and was mentally alert until a few days before the acute illness, when she told her pupils that 4 + 4 = 4, and her table manners were noticeably changed. Twelve hours before admission to the hospital she had had several convulsive seizures.

When she entered the hospital she was slightly confused and somewhat aphasic, but insisted that her illness was only a slight one and attempted to carry on a conversation, which, however, because of her confusion and disorientation, was limited to simple subjects. There was a definite cardiac arrhythmia and a faint

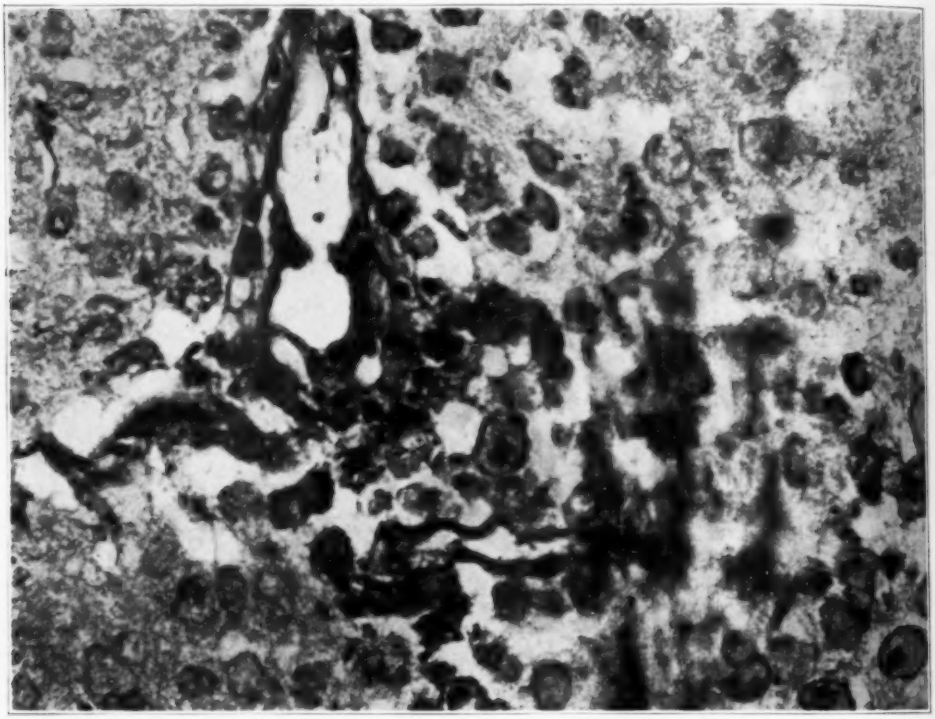


Fig. 20 (case 20).—A section taken from the discolored area shown in figure 19. Note the destruction of the wall of the small vessel and the alteration of the nerve elements surrounding it. Reduced from × 500.

systolic murmur was heard at the apex. The blood pressure was 135 systolic and 60 diastolic. The pupils were equal and reacted to light and in accommodation, and the fundi showed no evidence of pressure. There was no disturbance of the other cranial nerves. The deep reflexes were present but sluggish, and the Babinski sign was negative on both sides. A lumbar puncture showed clear cerebrospinal fluid under normal pressure. The cell count in the spinal fluid was 6 cells per cubic millimeter, and the Wassermann reaction was negative. The temperature range was from normal to slightly above.

The patient improved slightly during the first week, but during the second week there was evidence of greater cardiovascular difficulty, associated with the signs of hypostatic pneumonia, and the mental disturbance was more marked. The patient was in a stupor most of the time and when awake was very combative, refused to take food and insisted on getting out of bed. This condition continued without further evidence of neurologic disturbance until the eighteenth day, when she died.

Postmortem examination of the brain showed marked thickening of the pia-arachnoid, which was removed with the blood vessels from the entire cerebrum. The larger vessels showed very slight evidences of arteriosclerosis. A careful search was made for a thrombosed vessel, but none was found. The surface of

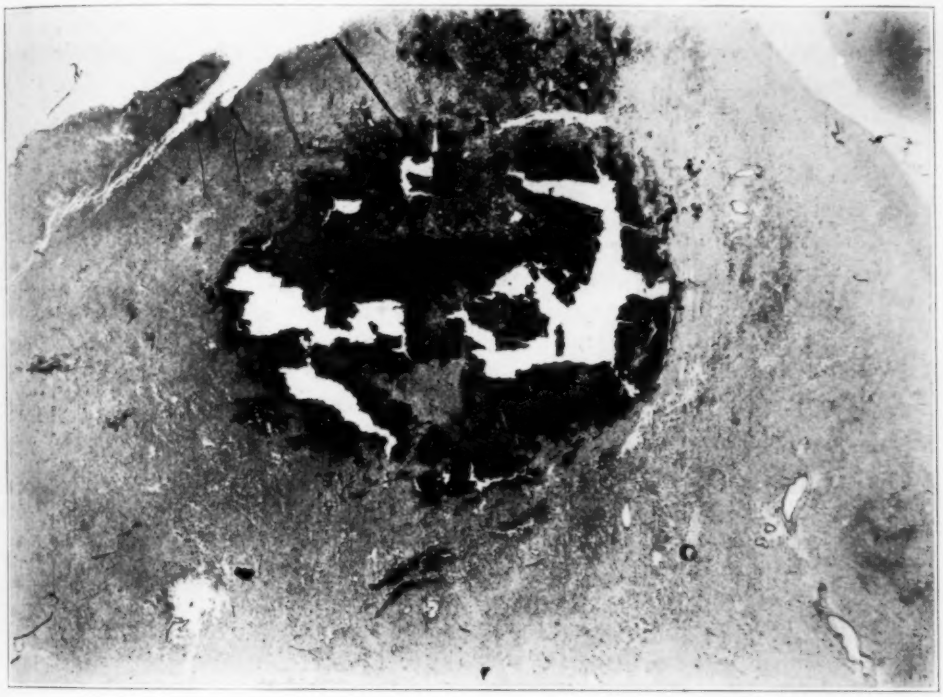


Fig. 21 (case 20).—This section was also taken from the discolored area at *A* in figure 19, and is an example of the numerous small hemorrhages that occurred in the area of the softening. This is the largest hemorrhage found and probably differs only in size from the large fatal clots following angiospasms as described by Westphal. Reduced from × 10.

the brain appeared normal, except in the posterior portion of the left inferior frontal convolution where there was an area of acute softening about the size of a half-dollar.

A horizontal cut was made through the center of this soft area and revealed small areas of hemorrhagic extravasation as shown in figure 19. Microscopic study of this softened cortex showed extensive changes, ranging from alterations of small vessels with perivascular nerve tissue alterations (fig. 20) to a small focus of hemorrhage (fig. 21).

Westphal emphasized that there is a great variation in the amount of blood that extravasates, depending, of course, on the degree of destruction that takes place in the vessel wall and surrounding tissue. The difference between this case and a case with massive bleeding I think is merely one of degree.

Particular attention should be called to the cases grouped under type D; first, because the lesions are superficial in the cortex (figs. 14, 15, 16 and 17); second, because of the relatively early age at which the hemorrhages occur, one in the second decade, three in the third, one in the fourth and two in the fifth, the oldest patient being 58 years; and third, because three of the five patients of this group who were operated on recovered and two (cases 15 and 17) are carrying on their usual occupations, eight and two years, respectively, after the operation. The third (case 16) is steadily improving five months after the operation. The fourth (case 13) died of pneumonia ten days after the operation, while the fifth (case 14) derived no benefit from the operation.

The surgical interest in this type of lesion was first aroused by the cases of superficial bleeding that were found at autopsy. The ages of these patients are certainly a matter of great importance, for persons under 50 years of age, unlike those of advanced age, are not so likely to be invalids after recovery following a cerebral accident of this type. This fact, I think, is borne out in my own cases.

Diagnosis is possible and depends on a sudden onset with gradually increasing symptoms, and should be no more difficult than the diagnosis of an abscess, simple cyst, tumor or traumatic blood clot in these areas. From the standpoint of operation one must endeavor to locate the lesion and evacuate the contents. Obviously, a procedure of this sort during the first stages might precipitate more bleeding. If the active bleeding has taken place, the removal of a firm blood clot may entail more operation than the patient will stand. Another factor that tends to delay operation in these cases is the fact that patients with simple cerebral apoplexies of this type often recover, and one hesitates to interfere with what might terminate favorably if left alone. There is, therefore, only one type left for the surgeon, those cases in which spontaneous recovery seems impossible. The most serious late symptom is increased intracranial pressure, which in the patients whom I have operated on has become alarming during the second week. This increase in pressure may, of course, be due to renewed bleeding, but in the patients whom I have operated on there was no evidence of recent bleeding and the serious change in the degree of pressure has been associated with a reaction of the brain surrounding the focus of bleeding.

In the beginning the focus has the appearance of coagulated blood. Within a few days this clot begins to liquefy, and by the end of the second or third week one finds the first stage of an apoplectic cyst, and the liquefaction of the clot. This, indeed, is quite similar to the train of events seen in the development of abscesses of the brain, the increase of intracranial pressure reaching a serious level at the time the abscess is well walled off and contains pure pus, which is easily drained through a cannula.

A review of my operative cases demonstrates the process of liquefaction and I think may be helpful in the determination of the choice of time for the operation.

For example, in case 14 the operation was undertaken three days after the onset of symptoms indicating a serious intracerebral bleeding. Dark thick tarlike blood was encountered, but did not escape through the cannula; the removal of the clot would have necessitated an extensive destruction of the brain and was therefore abandoned. The patient died on the following day.

In case 13 of this type the patient presented serious signs of increased intracranial pressure on the sixth day. Exploration of the focus of bleeding in the left temporal lobe (fig. 13) showed a large amount of liquefied blood clot with some solid blood clot. After removal of the liquid portion a sufficient amount of the clot was removed to reduce entirely the increased tension. Following the operation the cerebral symptoms were improved, and the condition seemed favorable until the development of pneumonia from which the patient died in ten days.

In case 15 there was a gradual onset of symptoms until the tenth day, when there was evidence of a serious degree of intracerebral pressure. A needle introduced into the focus at this time resulted in the free evacuation of 30 cc. of dark liquid blood. In addition to this a small decompression was done, and the patient made a very satisfactory recovery.

In case 16 an operation was performed fourteen days after the onset of the trouble because of the serious signs of increased intracranial pressure and complete paralysis of the opposite side of the body; 40 cc. of dark liquid blood was removed. This was immediately followed by improvement in the symptoms. The aspiration of 19 cc. of fluid from the original focus five months after the first operation indicates the formation of an apoplectic cyst in spite of the original aspiration. I therefore think that, in this case at least, benefit would have been derived from a second aspiration perhaps a month after the first.

The completely formed apoplectic cyst was found in case 18. This patient had presented cerebral symptoms one year prior to the cere-

bellar apoplexy which caused his death, and the cyst was found during the postmortem examination. At this time it contained dark brown fluid surrounded by a very definite wall (fig. 14).

SUMMARY

The paper includes twenty cases, nineteen of which fall into four clinical groups of spontaneous cerebral bleeding.

Under type A, meningeal bleeding, three cases in patients, whose ages were 33, 40 and 50 years, are described. Treatment in two, in which the patients recovered, was occasional lumbar puncture; while in the third a right subtemporal decompression late in the course was also done for more complete drainage of fluid. This patient died later following a large hemorrhage from the kidney. A complete autopsy was done and the partially healed internal carotid artery, the seat of the cerebral bleeding, is shown.

Under type B, meningeal bleeding, six cases, in which the ages of the patients were 22, 28, 41, 47, 51 and 60, are given. These cases were selected for pathologic study, and the point of fatal bleeding is illustrated in each case.

Under type C, intracerebral bleeding, three cases, in patients aged 27, 41 and 48, are given. All three had large deep-seated hemorrhages; in one, (age 27), the hemorrhage occurred during labor; in another (age 41), it occurred as a final episode after five years of vascular hypertension. In the third case, that of a man aged 48, there was a large deep-seated hemorrhage in the left hemisphere with no histologic evidence of a tumor, though the patient had had jacksonian attacks for twenty-two months, and exploration was made with the belief that blood had escaped into a tumor during a severe convulsive seizure just prior to admission.

Under type D, intracerebral bleeding, are seven cases in patients aged, respectively, 14, 34, 35, 39, 43 and 58. In five of these cases a clinical diagnosis of hemorrhage in the cerebrum was made and the diagnosis was verified at operation in four cases. In the fifth case the hemorrhage was not located at operation, but the patient made a satisfactory recovery after subtemporal decompression. Three of the five patients operated on recovered and two died.

In two cases of this type the hemorrhage was in the cerebellum. In one of these the diagnosis was made prior to death; in the other it was not suspected. The hemorrhage was in the cerebellar hemisphere in both cases and the patients died as the result of increased pressure; both probably would have been benefited by evacuation of the blood.

An additional case (case 20) is included in the discussion for the purpose of illustrating early changes in small blood vessels and beginning softening secondary to angiospasm, processes that in some cases preceded massive cerebral hemorrhage.

CONCLUSIONS

Spontaneous cerebral bleeding, whether from meningeal or intracerebral vessels, is often the result of rupture of an aneurysm, which may vary in size from a fraction of a millimeter to several millimeters in diameter. Arteriosclerosis is the most common cause of these aneurysms, but syphilis, trauma, bacteriologic reactions and congenital defects of the arterial walls are responsible for the lesion in some cases, or the bleeding may be due to a direct rupture of an arteriosclerotic or a congenitally weak vessel wall without aneurysmal formation.

Careful neurologic examination and grouping is essential so that the proper type of therapeutic procedure may be chosen.

In the treatment of these patients three conditions must be considered: (1) a sterile meningitis produced by the irritating effect of blood in the cerebrospinal fluid; (2) increased intracranial pressure produced by intracerebral or extracerebral clot; (3) disturbance of the cardiorespiratory and thermoregulatory centers seen in extensive extravasations or large clots at the base with destruction of the basal ganglia and rupture into the ventricle. The patient with the third symptomatology cannot be benefited surgically.

Theoretically, blood in the cerebrospinal fluid, as well as intracerebral and extracerebral clots following spontaneous cerebral rupture, should be removed, as in traumatic cases, in the hope of shortening the duration of the illness or preventing a fatality.

In traumatic cases in which there has been a tear of a normal vessel wall there is within a short time complete occlusion of the vessel with little likelihood of recurrent bleeding, but the possibility of recurrent bleeding in these cases of spontaneous rupture in which the outflow of blood is stayed only by a recent clot makes the early removal of the blood a complex question. The removal of the blood, in some cases at least, must be undertaken only as a means of controlling the more serious symptoms, allowing the patient to go through a tedious course of meningeal irritation or increased intracranial pressure until such time as the clot in the ruptured vessel becomes organized and effectively plugs it.

Subarachnoid drainage is useful in the cases in which the blood is washed into the cerebrospinal fluid, but should never be undertaken in cases showing evidence of large blood clots. If a clot exists the patient recovers spontaneously or the symptoms progress, demanding removal of the clot.

Superficial localized clots can be removed through a craniotomy, a procedure in many cases contraindicated by the poor general condition of the patient and the possibility of recurrent bleeding, or by aspiration of the blood through a small trephine opening. Aspiration can be accomplished under local anesthesia, but must be delayed until there is beginning cyst formation; in my cases it has not been followed by further bleeding. If the clot cannot be localized, serious symptoms of increased intracranial pressure may be relieved by a decompression.

Finally, I wish to emphasize that spontaneous cerebral hemorrhage is a common accident and may occur at any age; it must be taken into consideration in the differential diagnosis of a large number of intracranial disorders. Treatment in properly selected cases, especially in young persons, is followed by satisfactory results.

BRAIN CHANGES IN MALIGNANT ENDOCARDITIS

I. B. DIAMOND, M.D.
Assistant Professor of Neurology, University of Illinois College of Medicine
CHICAGO

Histologic examination of the central nervous system in malignant endocarditis reveals a rather common involvement of the brain which is The present study comprises twelve cases of malignant endocarditis that were placed at my disposal by Dr. R. H. Jaffe from his necropsy material at the Cook County Hospital and one case of rheumatic endocarditis from the Research and Educational Hospitals of the University of Illinois. They all showed manifest circumscribed, as well as diffuse, lesions which, though they varied to some extent, had certain common features which will be described.

REPORT OF CASES

CASE 1.—*Malignant endocarditis of several months' duration following rheumatic endocarditis; glial nodules in the pons, optic thalamus and subcortical white matter; diffuse glial proliferation; areas of rarefaction around blood vessels; degenerative changes of ganglion cells; hyperemia and mild perivascular infiltration of the pons; hyperplasia of the leptomeninges.*

History.—A white man, aged 42, a goldsmith, left the Cook County Hospital on Aug. 31, 1929, with a condition diagnosed as "chronic rheumatic and subacute bacterial endocarditis." He returned two weeks later complaining of recurrent chills, dyspnea, cough, nausea, vomiting and hematemesis.

Examination and Course.—The patient appeared anemic and acutely ill. The lungs revealed dulness at the bases with increased fremitus and râles. Double mitral and diastolic murmurs were present; the second pulmonic sound was accentuated. Petechiae developed over the deltoid region and back. Urinalysis showed albumin, 3 plus. Examination of the blood revealed: hemoglobin, 10 per cent; red cells, 2,560,000, and white cells, 5,800. The fever was of a septic type until Oct. 4, 1929, when the temperature became normal. The patient died on Nov. 5, 1929.

Necropsy (Dr. R. H. Jaffe).—The following anatomic diagnosis was made: thrombo-endocarditis of the aortic valve; chronic rheumatic endocarditis of the mitral and aortic valves, with insufficiency; eccentric hypertrophy of the heart and parenchymatous degeneration of the myocardium; a recent fibrinous pericarditis; subacute tumor of the spleen; chronic passive congestion of the lungs and liver;

Submitted for publication, Feb. 20, 1931.

From the Division of Neuropathology (service of Dr. Hassin) of the pathology laboratories of the Research and Educational Hospitals of the University of Illinois.

ascites, and bilateral hydrothorax. Culture of the blood taken from the heart revealed a growth of Streptococcus hemolyticus.

Examination of the brain revealed no macroscopic changes.

Microscopic Examination.—The outstanding histologic features were circumscribed foci or nodules of varied size, scattered in the white substance, optic thalamus and pons (fig. 1). The cells of the nodules were mostly glial elements,

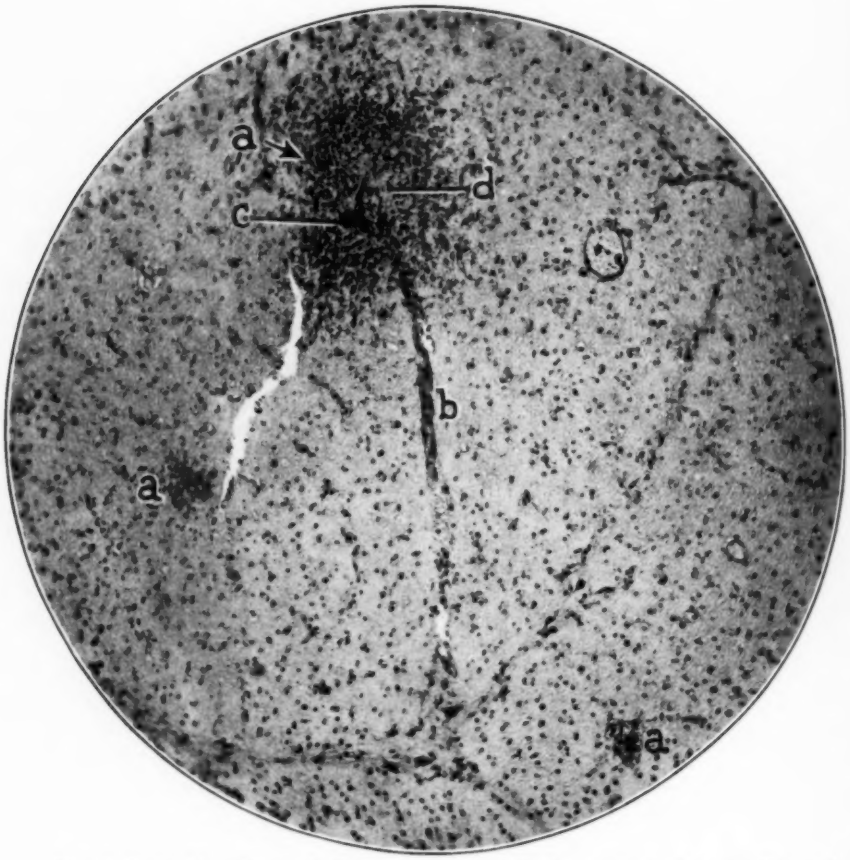


Fig. 1 (case 1).—Pons; (*a*) glial nodules; (*b*) blood vessel; (*c*) swollen and proliferated endothelial cells; (*d*) necrosis. Toluidine blue stain; low power magnification.

irregular in shape; their cytoplasmic processes were often fused, forming a loose syncytial structure. Mitotic figures were frequently noted, but micro-organisms were not seen (fig. 2, *a*). Occasionally a small vessel or capillary occupied the center of the nodules, though blood vessels could always be found near or within the nodules in serial sections (fig. 1, *b*). The vessels were usually proliferated, especially the endothelial layers (fig. 1, *c*). The tissue adjacent to the vessel appeared edematous or rarefied and often necrotic (fig. 1, *d*). The adjacent vessels were also proliferated. Many were congested or filled with

polymorphonuclear leukocytes and lymphocytes, while some exhibited mild perivascular lymphocytic infiltrations.

The parenchyma showed moderate edema throughout. Rarefaction was marked around the smaller blood vessels. The ganglion cells in such areas appeared diminished in number, and as a rule showed degenerative changes. In some, chromatolysis and neuronophagia were marked The glia cells were increased in number, mostly as glia nuclei (oligodendroglia) and rod cells

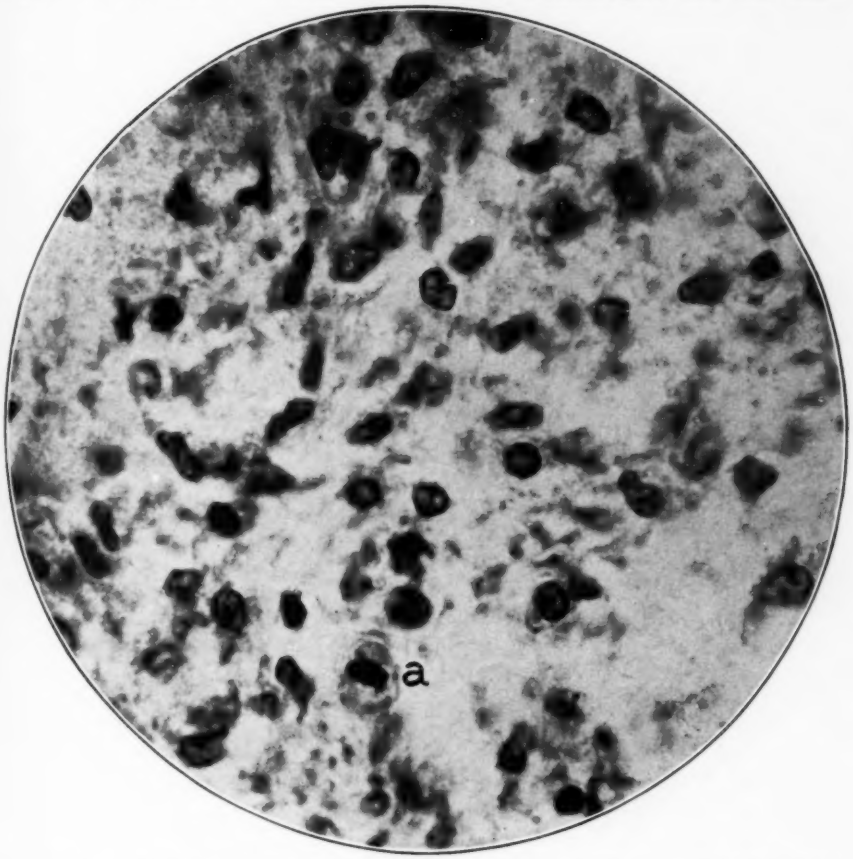


Fig. 2.—Glia cells from nodule, figure 1; (*a*) mitotic figure. Toluidine blue stain; oil immersion lens.

(microglia). Satellites were numerous around the smaller vessels and capillaries.

The pia-arachnoid was more or less thickened and hyperplastic in spots. Other portions were infiltrated with lymphocytes, polyblasts and fibroblasts, at times intermingled with erythrocytes, polymorphonuclear leukocytes and mesothelial cells. The pial blood vessels were congested; some appeared thickened, and a few were thrombosed. The stroma of the choroid plexus was edematous. The tuft cells were swollen and granular, and the vessels were congested and filled with polymorphonuclear leukocytes and lymphocytes.

CASE 2.—*Malignant endocarditis for seven months; glial-mesodermal nodules; bacterial emboli, with glial reticulum and necrosis; diffuse glial proliferation, especially in the pons and medulla; vascular proliferation and perivascular lymphocytic infiltration; degeneration of the ganglion cells; hyperplasia of the leptomeninges.*

History.—A white man, a laborer, aged 49, entered the Cook County Hospital on Oct. 16, 1929, because of pain in the left side of the chest on exertion, weakness in the legs, palpitation and cough of seven months' duration.

Examination and Course.—The patient was somewhat emaciated and dyspneic. The temperature was 97 F.; the pulse rate was 84, and the respiratory rate, 24. There were moist râles at the bases of the lungs. The heart was enlarged; systolic and diastolic murmurs were heard at both the apex and the base. Examination of the blood showed: hemoglobin, 80 per cent; red cells, 3,250,000, and white cells, 8,600. On November 5, the hemoglobin was 65 per cent, and the leukocyte count was 14,200. Urinalysis showed a trace of albumin. Wassermann tests of the blood and spinal fluid gave negative results. Hemorrhages from the nose and bowels occurred, and petechiae appeared in the conjunctiva. The clinical diagnosis was bacterial endocarditis. The patient died on November 6.

Necropsy (Dr. R. H. Jaffe).—The following anatomic diagnosis was made: thrombo-ulcerative endocarditis of the aortic valve; eccentric hypertrophy of the heart, and severe parenchymatous degeneration of the myocardium; recent fibrinous pericarditis; hypostatic pneumonia of the lower lobe of the right lung; passive congestion and edema of the lungs; passive congestion and cloudy swelling of the liver; cloudy swelling of the kidneys, with multiple old anemic infarcts; acute septic tumor of the spleen, with recent and old anemic infarcts. Cultures taken from the heart blood showed long chains of streptococci with numerous involutive forms and Bacillus coli.

The leptomeninges of the brain were slightly thickened along the blood vessels, and small plaques were present in the basilar artery.

Microscopic Examination.—Nodules and bacterial emboli, with foci of necrosis, were the outstanding microscopic features. The nodules were distributed in the cortex, white substance, pons and medulla. They varied somewhat in size, shape and cellular content. The glial nodules were similar to those described in case 1. In the cortex they contained, in addition, proliferated adventitial cells, some lymphocytes and occasionally polymorphonuclear leukocytes (fig. 3). The nodules were found usually around medium-sized blood vessels, the walls of which were swollen and the adventitial layers proliferated and infiltrated. The bacterial emboli, which contained streptococci, were found in the cerebral white substance, optic thalamus and caudate nucleus, and less frequently in the pons and medulla. The smaller blood vessels and capillaries were often obstructed by the microbes, and were surrounded by marked glial reticulum. In some instances, the tissues were completely necrosed (optic thalamus and caudate nucleus). In these areas reactive phenomena were absent. In the pons and medulla there were marked proliferation of the glia and of the blood vessels and pronounced perivascular infiltration. The olivary bodies, especially, were involved and covered by a great number of glia nuclei and rod cells (microglia). The vessels were filled with lymphocytes, polymorphonuclear leukocytes, microorganisms and macrophages.

The ganglion cells exhibited changes similar to those described in case 1 and occasionally showed the presence of fat. Neuronophagia, satellitosis and increase in glia nuclei and rod cells were marked. There was a moderate edema,

and the oligodendroglia was swollen. As a rule, the blood vessels of the parenchyma and pia were congested; the capillaries were prominent and proliferated. A few medium-sized vessels showed hyaline degeneration. The pia-arachnoid was more or less distended, and in its meshes were a moderate number of lymphocytes, polyblasts, fibroblasts, macrophages and gitter cells. Some parts contained mesothelial cell clusters.

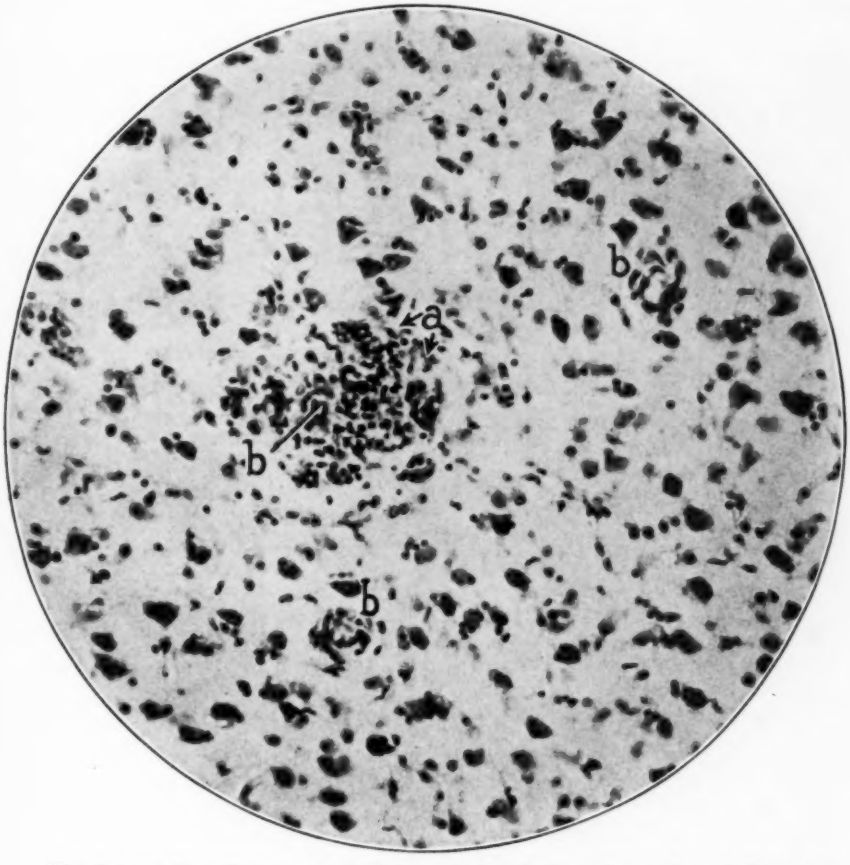


Fig. 3 (case 2).—Cortex; (*a*) nodule made up of glia and mesodermal elements; (*b*) vessel.

CASE 3.—*Malignant endocarditis for five months; marked emaciation, delusions, stupor and difficulty in swallowing; involuntary evacuations; glial, mesodermal and perivascular nodules; foci of softening in the cortex and basal ganglia (some in the process of organization); foci of necrosis with miliary-like abscesses secondary to septic emboli in the optic thalamus.*

History.—A white man, aged 62, a laborer, was admitted to the Cook County Hospital on July 26, 1929, because of dyspnea, precordial pain, weakness, cough and loss of weight; all of these symptoms were of about ten weeks' duration.

Five years previously he had had a "stroke" of moderate severity with paralysis in the right leg.

Examination.—The patient was emaciated; the gums revealed pyorrhea alveolaris; there were moist râles at the bases of both lungs; the heart revealed a rough systolic murmur at the apex and a systolic murmur at the base, especially over the aorta. The aortic sound was accentuated. The radial arteries were thick and beaded. The hemoglobin was 65 per cent; the red cells numbered

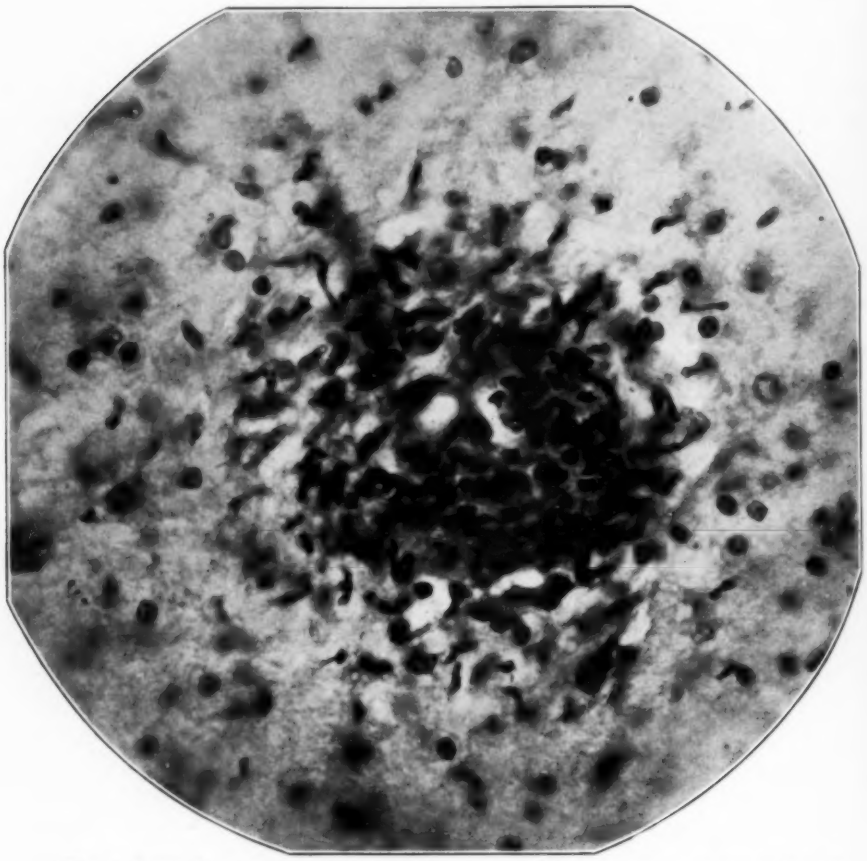


Fig. 4 (case 3).—Cerebral white substance; nodule, the majority are glia cells mixed with adventitial cells and lymphoid cells; the vessel is obscured by the proliferated cells. Toluidine blue stain; high power magnification.

2,770,000; the white cells, 12,250. Urinalysis showed no casts but many red blood cells. Cultures of the blood were sterile.

Course.—The patient had an irregular, septic type of fever, the temperature ranging from 99.5 to 103 F. Epistaxis and petechiae developed. At times the patient became irrational and stuporous; he had difficulty in swallowing and involuntary micturition and defecation. He gradually became weaker, and died on October 15.

Necropsy (Dr. R. H. Jaffé).—The anatomic diagnosis was: thrombo-ulcerative endocarditis engrafted on a chronic rheumatic endocarditis; slight stenosis of the mitral ostium; eccentric hypertrophy of the heart and advanced brown atrophy and parenchymatous degeneration of the myocardium; a huge septic infarct and inflammatory softening of the spleen; diffuse atheromatosis of the aorta; subacute glomerulonephritis with arteriolosclerosis and arteriosclerosis; small medullary abscess of the right kidney perforating into an interlobar artery; cloudy swelling and brown atrophy of the liver; severe hypostatic hyperemia and

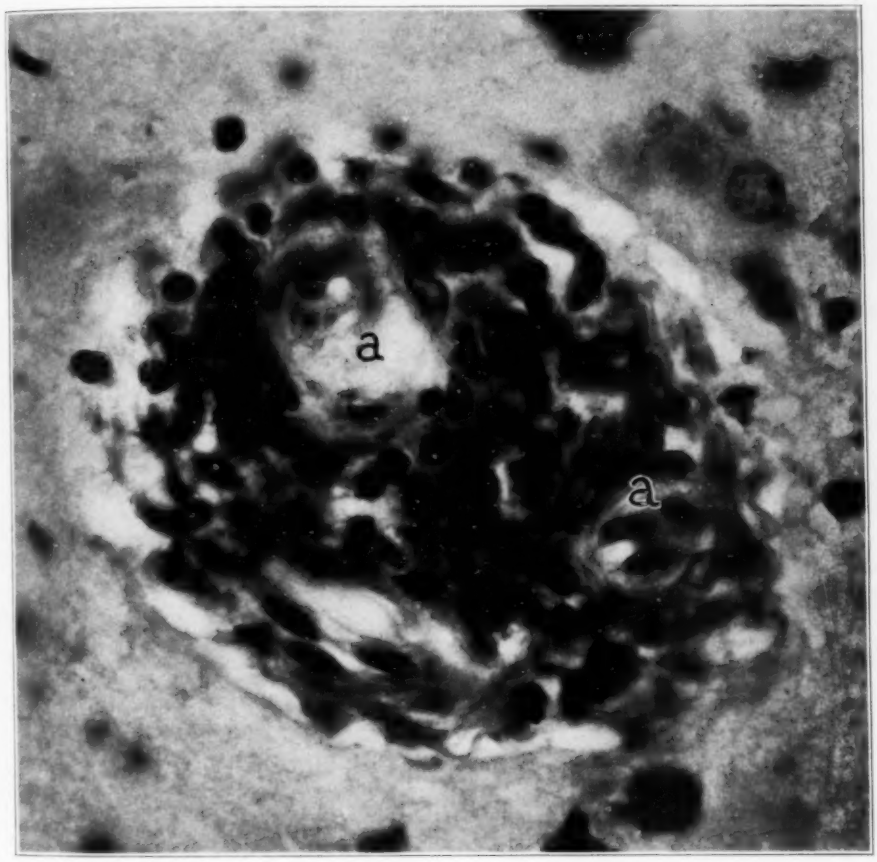


Fig. 5 (case 3).—Cortex; perivascular nodule; (*a*) the vessel is empty and degenerated. The proliferated adventitial cells and lymphocytes are confined to the perivascular space. Toluidine blue stain; oil immersion lens.

edema of the lungs; fibrous obliteration of both pleural cavities and cachexia. The weight was 93 pounds (42.2 Kg.).

Examination of the brain revealed no gross changes.

Microscopic Examination.—There were nodules, foci of softening and necrosis resembling miliary abscesses.

The nodules were found scattered in the cortex, the white substance of the different lobes, the basal ganglia and the pons. They were similar to the glial and

glial-mesodermal nodules described in cases 1 and 2, but they were occasionally of larger size (fig. 4). Others were situated about the smaller vessels of the cortex; they consisted mainly of proliferated adventitial cells, with some lymphocytes within the perivascular spaces (fig. 5). They resembled somewhat perivascular lymphocytic infiltrations, but differed from the latter in their rather gradual process of formation. A few contained multinuclear giant cells.

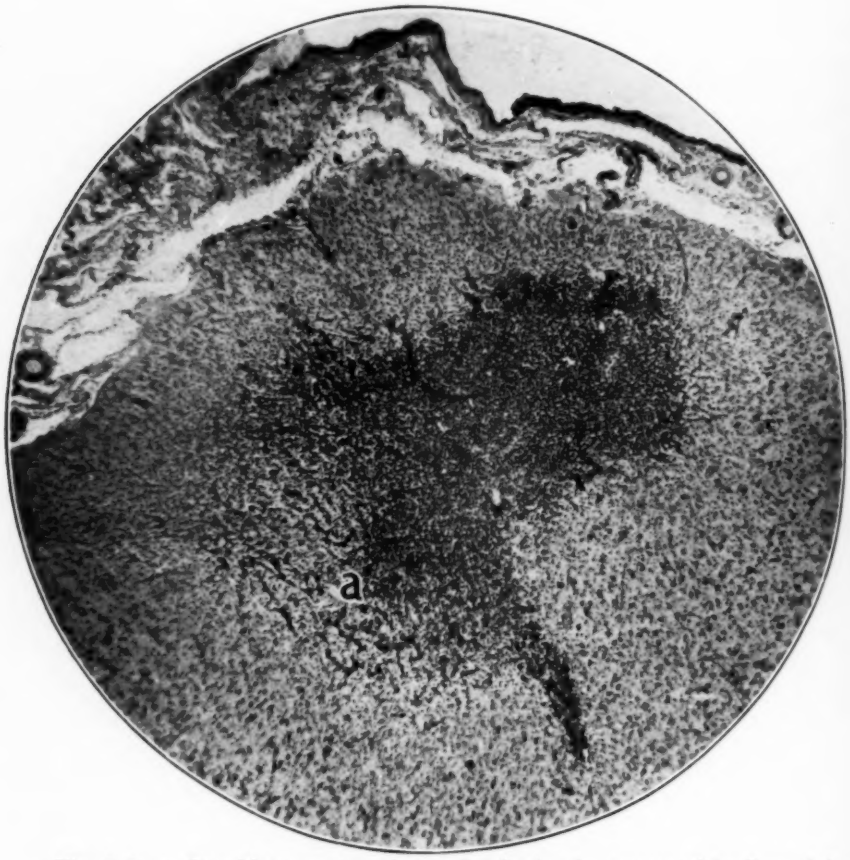


Fig. 6 (case 3).—Motor cortex; focus of softening in process of healing; (*a*) capillaries. Toluidine blue stain; low power magnification.

The foci of softening were abundant in the cortex. They were larger than ordinary nodules, irregular and in the process of organization (fig. 6). Their structure and cellular content varied. They contained numerous capillaries, many of which were newly formed and were scattered in richly cellular areas. The majority of the cells were glia and microglia, with many gitter cells and macrophages laden with pigment granules. The ganglion cells contiguous to the softening were swollen and degenerated, and showed neuronophagic phenomena. Smaller foci of softening with gitter cells were also present in the basal ganglia, while the optic thalamus showed, in addition, numerous foci of necrosis with miliary-like abscesses which were probably due to emboli (fig. 7). The embolic

vessels were completely blocked by darkly stained cellular débris. The capillaries and smaller vessels were unusually prominent; their endothelium was swollen and often showed mitotic figures, and the adventitia was infiltrated with polymorphonuclear leukocytes. The lumina were packed with polymorphonuclear leukocytes, which were also scattered throughout the necrosed area. They were frequently enclosed within macrophages and appeared as foci that greatly

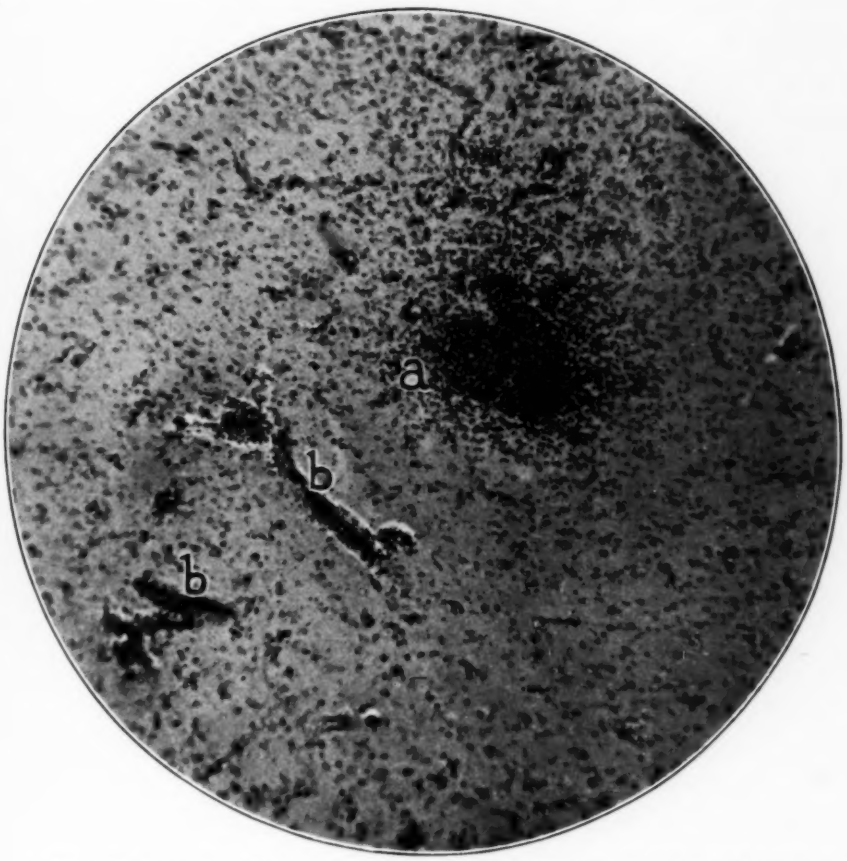


Fig. 7 (case 3).—Focus of necrosis; (*a*) collection of polymorphonuclear leukocytes; (*b*) plugged vessels containing cellular débris. Toluidine blue stain; low power magnification.

resembled miliary abscesses. Other foci were hemorrhagic and contained numerous macrophages laden with blood pigment granules and gitter cells filled with lipoids. The ganglion cells stained poorly and often appeared as shadows. The glia showed a marked reaction around the necrotic foci in the form of rod cells, satellitosis and cytoplasmic glia.

In the rest of the brain the glia generally exhibited progressive, proliferative changes, with prevalence of microglia cells (rod cell variety) and swollen oligodendroglia. The substance of the brain showed moderate edema and many areas

of rarefaction, especially around the blood vessels. The cortical ganglion cells presented acute changes. Some of the larger motor cells (Betz cells) were entirely devoid of Nissl granules; the cortical blood vessels were more or less congested, hypertrophied and proliferated, and the capillaries were prominent and increased in numbers.

The pia-arachnoid was greatly thickened, and in some areas hyperplastic. Scattered through the meshes were many lymphocytes, polyblasts and fibroblasts. In other areas the stroma was greatly distended and contained in its meshes, in addition to the aforementioned cells, macrophages, gitter cells and polymorphonuclear leukocytes. Mesothelial or arachnoid cells were especially numerous and formed clusters or nests. The pial vessels were congested and filled with polymorphonuclear leukocytes and lymphocytes; some were infiltrated and thickened, others showed sclerotic changes, and a few were thrombosed.

CASE 4.—*Malignant endocarditis for three months; syphilitic infection; no focalized cerebral symptoms; perivascular nodules, some containing giant cells; minute foci of softening and of necrosis.*

History.—A white man, aged 47, was admitted to the Cook County Hospital on April 2, 1930, complaining of dyspnea on exertion and swelling of the ankles of three months' duration. At the age of 14, he had had an attack of rheumatism, and at the age of 31 he had a chancre.

Examination.—Examination revealed dyspnea and cyanosis of the lips, ears and finger-nails. The heart was enlarged; systolic and diastolic murmurs were heard at the apex and a rough systolic murmur with an accentuated ringing second sound over the aortic area. There were cervical and brachial pulsations, a Corrigan pulse, Duroziez' sign and capillary pulsation. Petechiae of pinhead size were scattered over the abdomen, the lower extremities, the hands and the left anterior crural regions.

Laboratory Observations.—Urinalysis revealed considerable albumin, hyaline and granular casts and red blood cells. The hemoglobin was 60 per cent; the urea nitrogen, 23.35 mg. per hundred cubic centimeters of blood; the red cells numbered 2,320,000 and the white cells 7,000. The Wassermann and the formaldehyde gel tests gave positive results. Cultures of the blood showed Streptococcus hemolyticus.

Course.—The spleen became enlarged. Petechial spots appeared in the conjunctivae. Moist râles developed at the bases of the lungs; the temperature was irregular, and the pulse was increased to 150; the patient died on June 28, 1930. The clinical diagnosis was subacute bacterial endocarditis.

Necropsy (Dr. R. H. Jaffé).—The anatomic diagnosis was: thrombo-ulcerative endocarditis of the aortic valves; recent verrucous endocarditis of the mitral valves; parenchymatous degeneration of the myocardium with dilatation of all cardiac chambers; subacute splenic tumor, with old infarct scar; focal glomerulonephritis, arteriosclerosis and cloudy swelling of the kidneys; passive congestion and central focal necrosis of the liver; hyperemia and edema of the lungs; slight hydropericardium and ascites; focal fibrous pericardial adhesions, and fibrous obliteration of the right pleural cavity. Examination of the brain revealed no macroscopic changes.

Microscopic Examination.—Examination of the brain revealed numerous nodules, many of which were evidendly of recent origin; they were minute and confined to the perivascular spaces (motor area, caudate nucleus and optic thala-

mus). Under low magnification they appeared as vessels with intense perivascular infiltrations. They differed from the latter, however, in that the cell accumulations were usually localized at one area of the perivascular space, giving the vessels a bulged appearance. The cells were mainly proliferated adventitial cells, mixed with a few lymphocytes. Mitotic figures were occasionally seen. The adventitial layers were thickened and merged with the cells of the nodules, often compressing the lumina of the vessels. An unusual feature was the presence of giant cells within the nodules; they were situated at the periphery. Other nodules were similar to those described in the previous cases and were scattered in the cortex, white substance, pons and olivary bodies of the medulla. Foci of softening and necrosis were also present, some of which were in the process of organization. These foci were scattered in the optic thalamus and in the substantia nigra. The blood vessels in the basal ganglia, pons and medulla showed a mild perivascular infiltration, while some of the vessels in the caudate nucleus showed hyaline degeneration, and a few contained streptococci. The brain tissue was edematous, and some of the ganglion cells showed marked degenerative changes with neuronophagia; the glia was diffusely proliferated; microglia cells were also increased, and around the foci of softening and necrosis a glial reticulum was in evidence. The meninges exhibited the same hyperplastic phenomena as those described in the other cases.

CASE 5.—*Malignant endocarditis for about one month; clinical signs of meningitis; focal and diffuse inflammation with perivascular leukocytic and lymphocytic infiltrations; hyperplasia and infiltration of leptomeninges; glial-leukocytic nodules, containing micro-organisms.*

History.—A colored woman, aged 29, was admitted to the Cook County Hospital on Jan. 6, 1930, complaining of pain and stiffness in the neck, pains in the right ear and difficulty in swallowing of only a few days' duration; four weeks previously she had had chills and fever.

Examination and Course.—The temperature was 100 F.; the pulse rate was 124, and the respiratory rate was 32. The neck was stiff. The pupils were equal and regular and reacted to light and in accommodation. The right side of the soft palate was weaker than the left. The lungs were normal, but some apical dulness developed. The heart tones were regular; there was a thrill at the apex, with a systolic murmur. A Babinski sign was present on the left; Kernig and Brudzinski signs were also present at first, but became negative on subsequent examination. The white cell count was 21,000. The spinal fluid was clear and contained 350 cells per cubic millimeter, of which 80 per cent were polymorphonuclears.

The temperature was of a septic type. No definite diagnosis was made, but the possibility of an abscess of the brain was considered. Death ensued on Feb. 6, 1930.

Necropsy (Dr. R. H. Jaffé).—The following anatomic diagnosis was made: thrombo-endocarditis of the mitral valve "on the base of an old rheumatic endocarditis," parenchymatous degeneration of the myocardium and kidneys; septic infarcts of the spleen, with extensive softening; multiple septic infarcts of the left kidney; focal bronchopneumonia of the upper and lower lobes of the right lung, and confluent bronchopneumonia of the middle lobe; hyperemia and edema of the lungs; purulent otitis media on the right side; brown atrophy and cloudy swelling of the liver; decreased lipoid content of the suprarenal cortex; petechial hemorrhages of the skin and conjunctivae, and emaciation.

Bacterioscopic Examination.—From the middle ear were obtained long chain (streptococci) and gram-positive diplococci (a type of pneumococcus); from the softened infarct of the spleen, degenerated streptococci and better preserved staphylococci.

The brain weighed 1,250 Gm. The convolutions were flattened, and the sulci were narrow. The left parietal prominence and the right hippocampus bulged markedly. The right middle cerebral artery was completely occluded by a laminar,

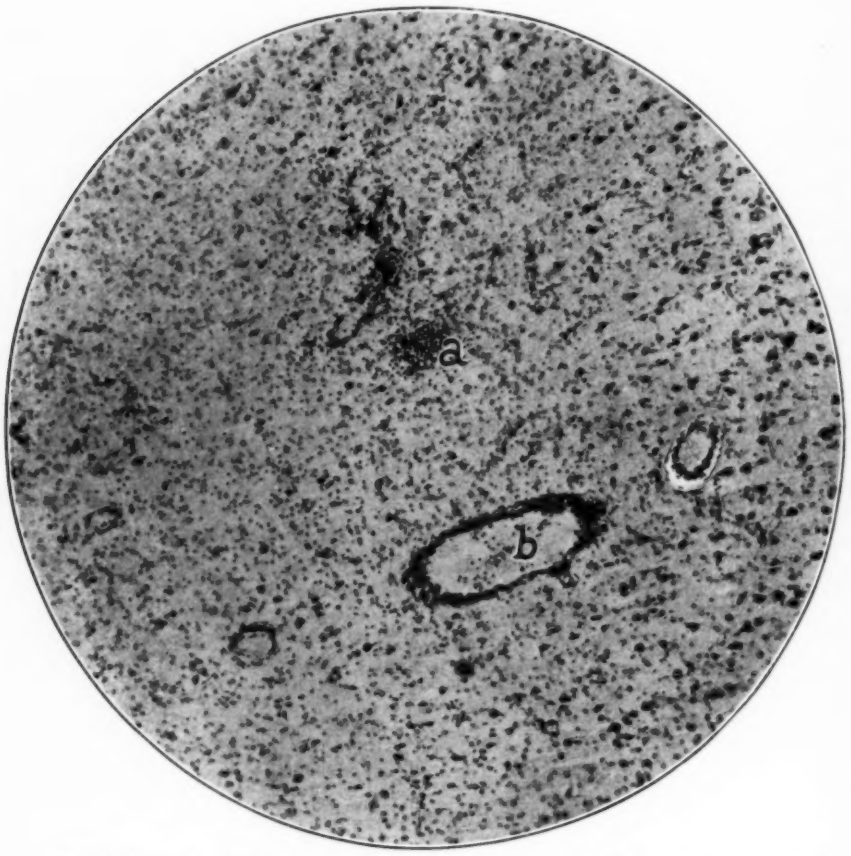


Fig. 8 (case 5).—Region of deeper layer of cortex and white substance. Acute diffuse encephalitis; (*a*) glial-leukocytic nodule; (*b*) perivascular infiltration of vessels. Toluidine blue stain; low power magnification.

pinkish-red, granular clot, which extended to the anterior communicating artery and to the lenticulostriate artery.

Microscopic Examination.—There were numerous nodules with varied cellular contents. Some were glial, some were glial-mesodermal, but the majority consisted of a mixture of glial and hematogenous elements (glial-leukocytic nodules). In some, the polymorphonuclear leukocytes predominated; in others, the glia cells. In these nodules micro-organisms and, occasionally, many red blood cells

(hemorrhages) were present. The parenchyma was edematous or rarefied and frequently diffusely infiltrated with polymorphonuclear leukocytes (fig. 8). The latter were often enclosed within glia cells (fig. 9). The blood vessels, including those within the nodules, were congested, hypertrophied and filled with mononuclear and polymorphonuclear leukocytes, staphylococci and cocci in long chains. Some were completely blocked by leukocytic thrombi and bacterial emboli, causing necrosis of the surrounding tissue (basal ganglia). In some blood vessels all

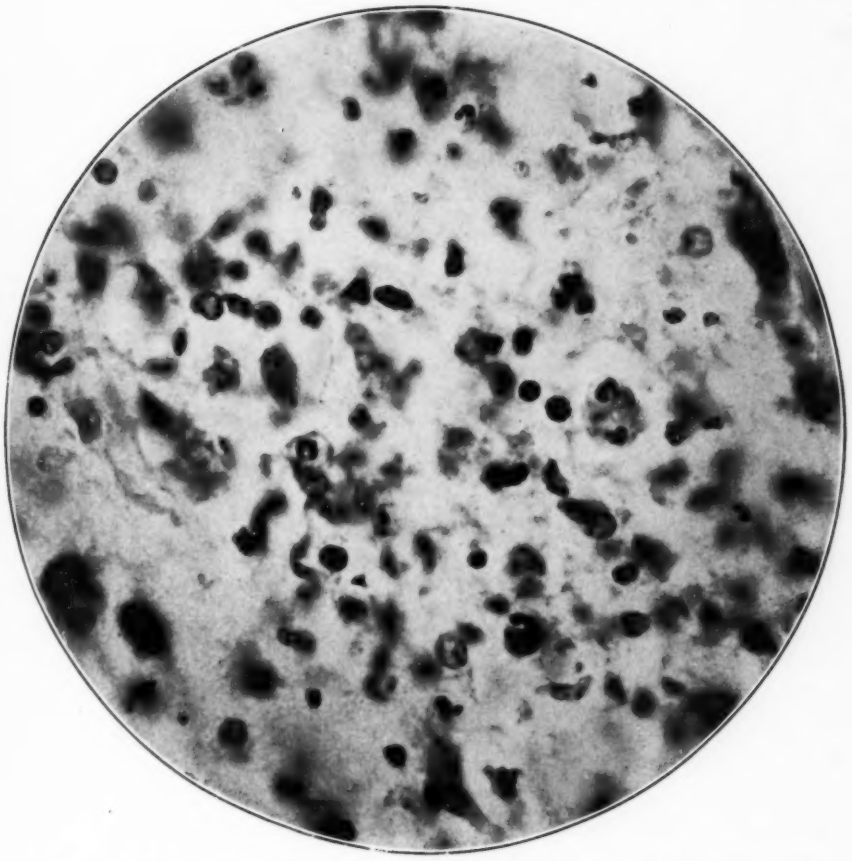


Fig. 9 (case 5).—Cortex. Acute diffuse encephalitis showing polymorphonuclear leukocytes within glia cells. Toluidine blue stain; oil immersion lens.

the layers were infiltrated with polymorphonuclears (panarteritis); in others only the perivascular lymph spaces exhibited marked infiltrations, mostly lymphocytes, a few plasma cells and proliferated adventitial cells. Mitoses in the last named cells were often noted. Some vessels were markedly changed; they appeared disrupted and the surrounding tissue necrotic and enveloped by a wall of glia cells. Such vessels strongly resembled nodules with central necrosis (fig. 10). The capillaries were also prominent and proliferated. The ganglion cells exhibited various degenerative changes, with marked neuronophagia. The glia was pro-

liferated; migroglia cells were numerous, with long and branched cytoplasmic processes. The oligodendroglia was swollen.

The changes outlined involved more or less the hemispheres, cerebellum, basal ganglia, pons and medulla. The meninges were equally affected. The meshes were greatly distended and infiltrated by various cellular elements. Polymorphonuclear leukocytes and lymphocytes were gathered in clusters around the vessels. Large and small mononuclear proliferated tissue cells were intermingled with macrophages, erythrocytes and pigment-laden phagocytes. The pial vessels were

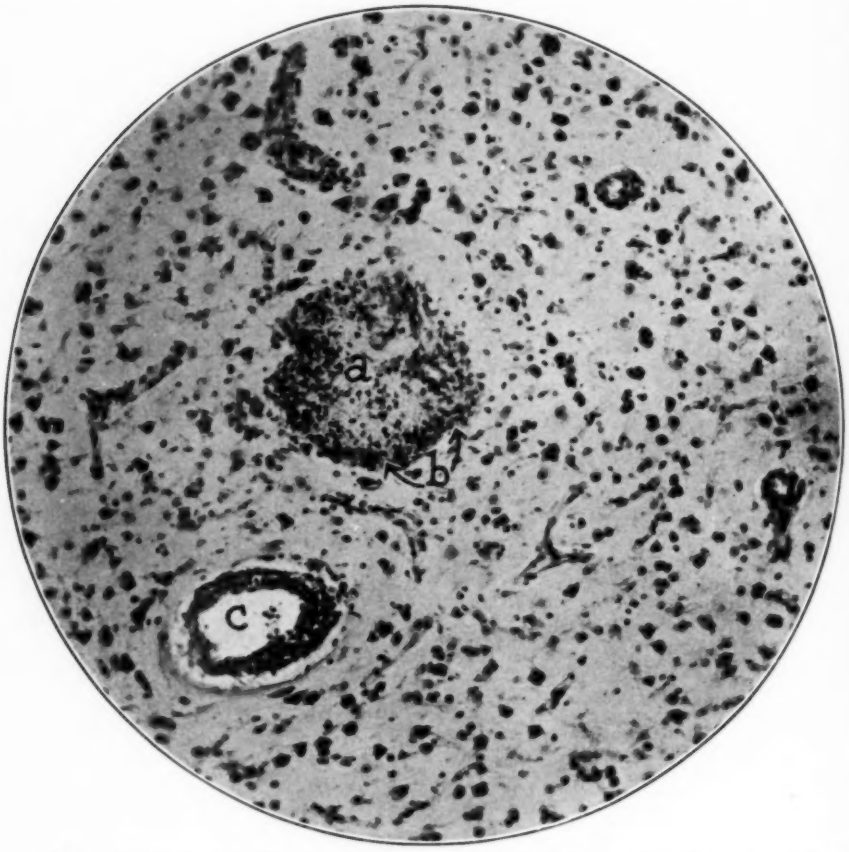


Fig. 10 (case 5).—Cortex; acute diffuse encephalitis. (*a*) disrupted vessels resembling a nodule with central necrosis; (*b*) glia wall; (*c*) vessels with marked perivascular infiltration. Toluidine blue stain; low power magnification.

hyperemic, and their walls were hypertrophied and infiltrated at times by polymorphonuclear leukocytes. Some were filled with clusters of leukocytes and dense masses of cocci, and some of the larger vessels contained leukocytic thrombi. The tuft cells of the choroid plexus were swollen and vacuolated; the stroma was edematous and moderately infiltrated, and the vessels were markedly hyperemic. The picture was that of acute meningo-encephalitis.

CASE 6.—*Malignant endocarditis for four months; symptoms of meningitis eight days before death; lesions in the brain similar to those in case 5.*

History.—A white woman, aged 57, was admitted to the Cook County Hospital on Feb. 12, 1930, and died five days later. The complaints were headaches, chills and fever, abdominal pains and diarrhea of three days' duration, loss of weight and weakness for four months and general failing in health for two years.

Examination and Course.—The temperature was of a septic type. The pupils were irregular. The heart and lungs appeared normal. Urinalysis showed a few granular and hyaline casts. On February 14, the temperature was 104 F., and moist râles were heard in the bases of the lungs. On February 15, the patient complained of severe headaches with marked rigidity of the neck. The Brudzinski sign was positive.

Necropsy (Dr. R. H. Jaffé).—The following anatomic diagnosis was made: thrombo-endocarditis of the mitral valve; embolism of the superior mesenteric artery, with recent hemorrhagic infarction of the lower two thirds of the ileum; embolism of the splenic artery with formation of a large, liquefied infarct; anemic infarcts in both kidneys and renal arteriosclerosis; cloudy swelling and fatty degeneration of the liver; petechial hemorrhages in the conjunctivae and in the pleura of the right lung.

On macroscopic examination the brain revealed only scattered petechial spots varying in size from that of a pinpoint to that of a pinhead.

Microscopic Examination.—Scattered throughout the brain were nodules, the cells of which were largely a mixture of polymorphonuclear leukocytes, macrophages and glial elements. Such foci harbored a great number of micro-organisms (cocci), many within macrophages. Other nodules were practically devoid of micro-organisms and consisted mostly of glia cells. The ganglion cells in the vicinity of the nodules were greatly changed, with marked neuronophagia. The vessels were infiltrated with lymphocytes and occasionally with polymorphonuclear cells. There was also marked proliferation of the adventitial and endothelial cells, which showed mitotic figures. In the optic thalamus a number of vessels were found incrusted with lime salts. Frequently, the smaller vessels and capillaries were filled with dense clusters of streptococci mixed with polymorphonuclear leukocytes and lymphocytes. The glia cells were markedly increased, and mitotic figures were often seen in them. Microglia cells were especially numerous around the nodules. The meninges exhibited cell infiltrations similar to those described in case 5.

CASE 7.—*Septicopyemia, following extraction of a tooth, that lasted three and a half months; malignant endocarditis found at necropsy; acute hemorrhagic encephalitis with extensive hemorrhages in the cerebellum; foci of softening; septic emboli; reactive phenomena of the glia; infiltrations of the blood vessels; hyperplasia of the leptomeninges.*

History.—A colored man, aged 28, entered the Cook County Hospital on July 11, 1930, after having complained off and on for two months of nausea and vomiting (more or less), which developed after extraction of a tooth. He gave a history of dyspnea for years, rheumatic fever fifteen years previously and cardiac decompensation three or four times since then.

Examination and Course.—There was a small ulceration of the gum at the site of the lower second molar on the right side. The lungs revealed a few

scattered râles. The heart showed a "mitral configuration," with presystolic and systolic murmurs at the apex and accentuated pulmonic sound. The pupils and the deep reflexes were normal.

The blood count revealed 3,200,000 red cells and 11,400 leukocytes. The Kahn and formaldehyde gel tests were negative. The temperature was of a septic type; arthritis of the elbows and wrists developed. On July 22, 1930, the spleen was tender; on August 28, the day of death, petechiae were found for the first time in the conjunctiva, the mucosa of the mouth, the trunk and over the extremities.

Necropsy (Dr. R. H. Jaffé).—The following anatomic diagnosis was made: thrombo-endocarditis of the mitral, aortic and tricuspid valves; eccentric hypertrophy of the heart and severe degeneration of the myocardium; subacute tumor of the spleen, with multiple anemic infarcts and a large septic one; fatty degeneration of the liver; cloudy swelling of the kidneys, with multiple anemic infarcts; focal bronchopneumonia in the lower lobes of both lungs; petechial hemorrhages in the skin, conjunctiva, lungs, mucosa of the renal pelvis, urinary bladder and stomach; submucous hemorrhages of the intestine; subpleural and dural hemorrhages; icterus; hydropericardium, slight ascites and anasarca of both lower extremities. A growth of gram-positive streptococci was obtained from the spleen.

The brain weighed 1,320 Gm. The convolutions were slightly flattened, and there were extensive extravasations of blood in the leptomeninges along the vessels over the convexity of both hemispheres. In the upper half of the right cerebellar hemisphere, there was an area of softening measuring 5 by 4 by 3 cm., containing dark red blood clots.

Microscopic Examination.—Focal and diffuse hemorrhages were scattered in the cortex, the basal ganglia and, especially, the cerebellum, often around greatly dilated and congested blood vessels; the perivascular spaces often contained polymorphonuclear leukocytes and macrophages laden with micro-organisms and granules of blood pigment. Extensive hemorrhages were also present in the cerebellum, where large areas of both the granular and the molecular layers were involved. Adjacent to them were foci of softening with many gitter cells, macrophages and cytoplasmic glia cells. The capillaries in these foci were prominent, with swollen and proliferated endothelium. The Purkinje cells were greatly degenerated.

In addition to the hemorrhages, nodules were also present. These were less numerous than the hemorrhagic foci. They consisted largely of polymorphonuclear leukocytes mixed with glia cells, and enveloped the smaller vessels. The walls of the latter were proliferated and infiltrated with leukocytes. Clusters of cocci were often present within macrophages, in the lumina of the vessels, in the perivascular spaces and in the adjacent parenchyma. Glial nodules were few and were present in the white matter, pons and optic thalamus. There was marked edema, with areas of rarefaction. The ganglion cells exhibited various stages of degeneration with neuronophagia. There was an increase in the glia nuclei and microglia cells. In the meninges were similar hemorrhages with vascular changes. Some blood vessels were infiltrated with leukocytes; a few were thrombosed with hyaline and leukocytic thrombi, and some were packed with embolic masses of cocci, free and within macrophages.

CASE 8.—*Malignant endocarditis for seven months; frequent convulsions before death; multiple minute foci of softening (some in the process of organiza-*

tion); proliferation of glia, mesoderm and pia-arachnoid; changes resemble those of septicemia.

History.—A white woman, aged 24, was admitted to the Cook County Hospital on Oct. 17, 1929, because of weakness in the left arm and leg for six weeks, shortness of breath, pains in the joints, cough, loss of weight and night sweats, all of four months' duration.

Examination and Course.—The left arm was much weaker than the right. A harsh systolic murmur replaced the first sound. Over the entire chest were heard sonorous, whistling and crepitant râles. The temperature was of a mildly septic type. Tender subcutaneous nodes developed on the hands and feet, and purpuric spots on the skin; the spleen became tender. Two months later, the patient complained of abdominal pains, vomiting, diarrhea, fever, cyanosis and severe headaches. The heart became enlarged and the pulse rapid (from 120 to 140 per minute). The red blood count became reduced to 2,600,000, and the hemoglobin dropped to 55 per cent. On Jan. 19, 1930, left-sided convulsions developed, with loss of consciousness for ten minutes. Such attacks occurred frequently during the last days before death, which occurred on January 26. At the time of death the weight was 82 pounds (37.2 Kg.).

Necropsy (Dr. R. H. Jaffé).—The following anatomic diagnosis was made: thrombo-endocarditis of the mitral valve, the posterior aspect of the left auricle and of the aortic valve; acute emphysema of the lungs, and diffuse suppurative bronchitis with subpleural bronchopneumonic areas in the lobes of the left lung; slight eccentric hypertrophy of both cardiac chambers; anemia and parenchymatous degeneration of the myocardium; subacute tumor of the spleen, with recent and old anemic infarcts; anemia and cloudy swelling of the kidneys, with a small recent infarct in the left; passive hyperemia and fatty degeneration of the liver; marked decrease of the lipoid content of the suprarenal cortex; slight ascites and bilateral hydrothorax.

In the right parietal lobe and posterior central convolutions of the brain there were recent and old foci of hemorrhages.

Microscopic Examination.—Minute multiple foci of softening were a striking feature in this case. Figure 11 illustrates clearly such a focus which affected, in parts, the granular layer of the cerebellum, the cells of which were greatly reduced in numbers. The area contained a number of prominent capillaries, with markedly swollen and proliferated endothelium. Many of the latter were in the process of budding and occasionally exhibited mitotic figures. The glia was also increased and proliferated. There were many gitter and glia cells, with irregular and elongated branched processes, with a tendency toward bushlike formations (Spielmeyer's Strauchwerk).

Other foci (motor area) were more cellular and rather compact and vascular. The general changes present throughout were those of edema, dilated and infiltrated Virchow-Robin spaces, moderate hyperplasia and perivascular infiltration of the blood vessels. The ganglion cells exhibited more or less degenerative changes, with marked neuronophagia. The glia generally was increased in the form of many glia nuclei and microglia cells. Glial nodules were rather few; glial clusters (rosette and stellate formations) were sometimes observed in the white substance, optic thalamus, pons and medulla. The oligodendroglia was swollen. In some parts the pia-arachnoid was hemorrhagic and contained many macrophages filled with granules of blood pigment. Some parts were hyperplastic and contained foci of mesothelial cells. Other parts were moderately dis-

tended, and the meshes were invaded by mononuclear cells, polyblasts, fibroblasts, gitter cells and polymorphonuclear leukocytes. The pial blood vessels were congested and filled with leukocytes.

CASE 9.—*Acute onset of malignant endocarditis, with death in seven days; focus of softening in the cortex; diffuse degenerative changes of ganglion cells; proliferation of glia, blood vessels and pia-arachnoid; changes resemble those of "acute toxic encephalitis."*

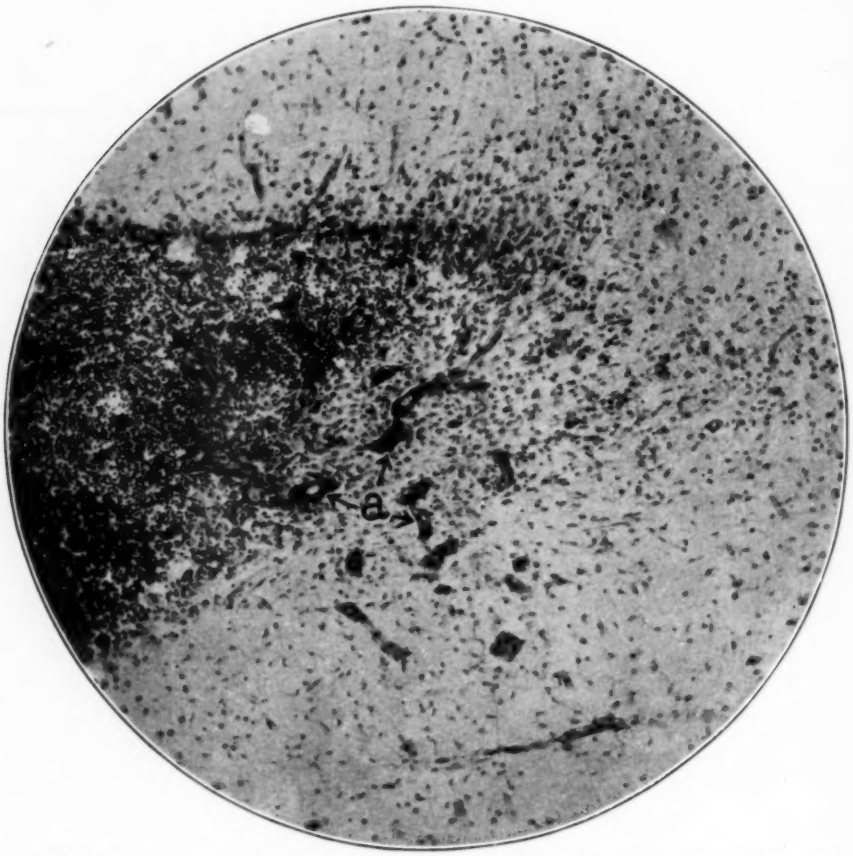


Fig. 11 (case 8).—Cerebellum; focus of partial softening of granular layer; (*a*) prominent and proliferated capillaries. Toluidine blue stain; low power magnification.

History.—An Italian woman, aged 40, was admitted to the Cook County Hospital on Aug. 29, 1930, because of pain in the left side of the chest, shortness of breath, palpitation and sore throat for several weeks. For two days prior to admission the patient had had chills, fever and vomiting.

Examination.—There were: systolic and presystolic murmurs at the apex, with the second pulmonic sound accentuated; roughened breathing; albuminuria (albumin, 2 plus); 70 per cent hemoglobin; 18,200 leukocytes. The formaldehyde gel test gave positive results for bacterial endocarditis.

Course.—The temperature was of a septic type, ranging from 98 to 104 F., preceded sometimes by chills; the pulse rate varied from 90 to 140 per minute. On September 1, small petechiae appeared on the right posterior pharyngeal wall. There was pericordial pain. Death occurred on September 6.

Necropsy (Dr. R. H. Jaffé).—The anatomic diagnosis was: thrombo-endocarditis of the mitral valve; parenchymatous degeneration of the myocardium; hydropericardium; multiple large infarcts of the kidneys; septic tumor of the spleen; focal glomerulonephritis; edema and hypostasis of the lungs; cloudy swelling and centro-acinar necrosis of the liver; focal fibrous adhesions in the right pleural cavity; a fibrocaseous, primary tuberculous nodule in the right pulmonary lobe and its draining lymph nodes; decreased lipoid content of the suprarenal cortices.

Brain: No gross changes were present.

Microscopic Examination.—There was a small focus of softening in the cerebral cortex. The area involved was swollen and contained only a few ganglion cells, which were markedly degenerated. The glia cells were abundant; some were round, some were elongated, many resembled Hortega cells and some showed transitions to gitter cells. The vessels were swollen, and the capillaries showed signs of new formation; budding of the endothelium was marked. A large vessel which occupied the center of the focus was greatly thickened because of swelling and proliferation of its layers; the adventitia exhibited mitotic figures, and in its spaces a few gitter cells were present. No micro-organisms were found. The brain throughout showed severe changes in the ganglion cells, with marked neuronophagia. There were edema and a marked glial reticulum. The glia was moderately proliferated. There was marked hyperemia of the blood vessels; many were filled with mononuclear and polymorphonuclear leukocytes, and some vessels (caudate nucleus) were plugged by dense leukocytic thrombi.

In some areas the meninges were hyperplastic; in other areas they appeared edematous. Between the meshes there were many red blood cells, fibroblasts, polyblasts, mesothelial cells, macrophages filled with granules of blood pigment and a few polymorphonuclear leukocytes. The pial vessels were hyperemic, but showed no other changes.

CASE 10.—*Syphilitic infection, cardiorenal disease and hypertension; twitchings of the face, loss of consciousness and right hemiplegia; death six months later from malignant endocarditis; areas of softening in the left hemisphere, pons and medulla; hyaline degeneration, sclerosis and thrombosis of cerebral and pial vessels; hyperplasia of glia, mesoderm and pia-arachnoid; degeneration of ganglion cells.*

History.—A man, aged 35, entered the Cook County Hospital on May 2, 1929, complaining of dyspnea, headaches, cough, weakness and dizziness of several weeks' duration.

Examination and Course.—The blood pressure was 238 systolic and 158 diastolic. The aortic second sound was "hollow" and transmitted downward; the systolic sound was short and blowing. There were edema of the lower extremities and petechiae over the cubital spaces. The hemoglobin was 65 per cent; the red cells numbered 3,070,000, and the white cells, 10,600. The Wassermann reaction of the blood was 3 plus, but on October 15 it was negative. Urinalysis showed albumin, 2 plus, and a few casts. A diagnosis of cardiorenal disease was made. On May 7, twitchings of the face and paralysis of the right side of the body (cerebral thrombosis) occurred, and the patient became unconscious. On July

5, coronary occlusion developed, and on July 29, a specific neuroretinitis. He died on Oct. 30, 1929.

Necropsy (Dr. R. H. Jaffé).—The following anatomic diagnosis was made: thrombo-ulcerous endocarditis of the mitral valve engrafted on a chronic rheumatic endocarditis; eccentric hypertrophy of the heart, with endocardial sclerosis; syphilitic aortitis; hemorrhagic infarct of the lower lobe of the right lung, with central softening; bronchopneumonia of the lower lobes of both lungs; chronic

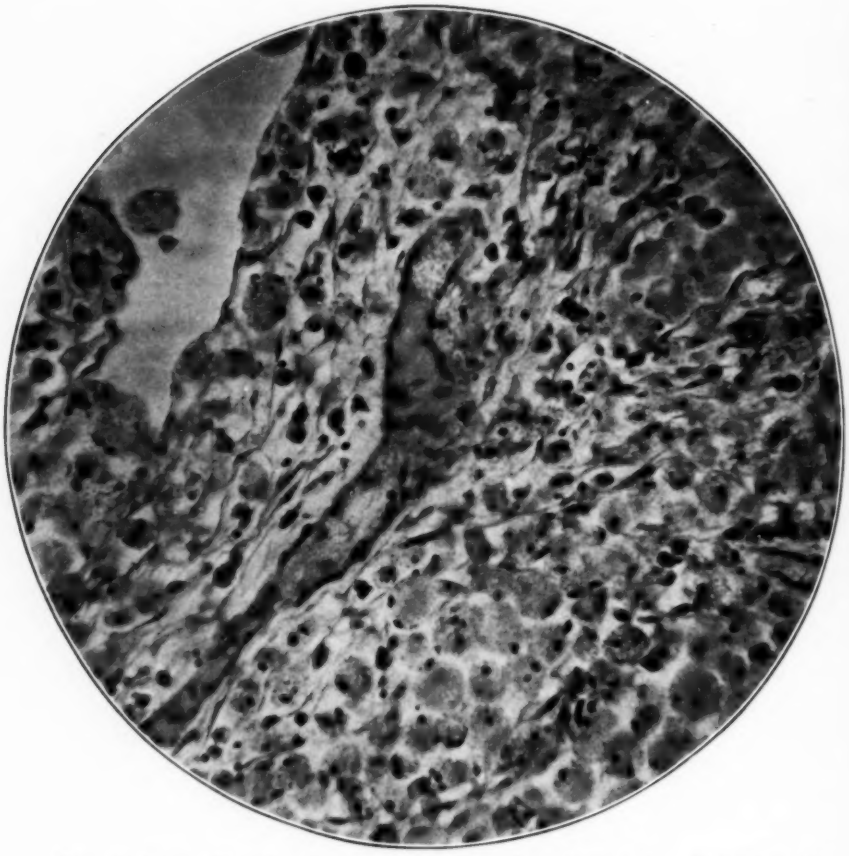


Fig. 12 (case 10).—Focus of softening showing gitter cells. Toluidine blue stain; high power magnification.

glomerulonephritis; subacute infections; splenic tumor; fatty changes and passive congestion of the liver, and serofibrinous pleuritis of the right side.

Brain: There was chronic edema of the leptomeninges. The basilar vessels showed atheromatous patches. There were grayish thickenings over the leptomeninges, from 2 to 3 mm. in diameter. In the left hemisphere, in the region of the insula Reili, was a circumscribed yellowish-brown area of softening, which involved the external capsule and the claustrum. It measured 25 by 0.8 by 5 cm., and extended anteriorly to the nucleus caudatus.

Microscopic Examination.—The outstanding changes were areas of softening and changes in the blood vessels (hyaline degeneration, sclerosis and thrombosis) with foci of necrosis. Nodules were few and were rather limited to the white substance.

The substance of the brain involved in the softening was completely replaced by gitter cells (fig. 12), some of large size, macrophages laden with pigment

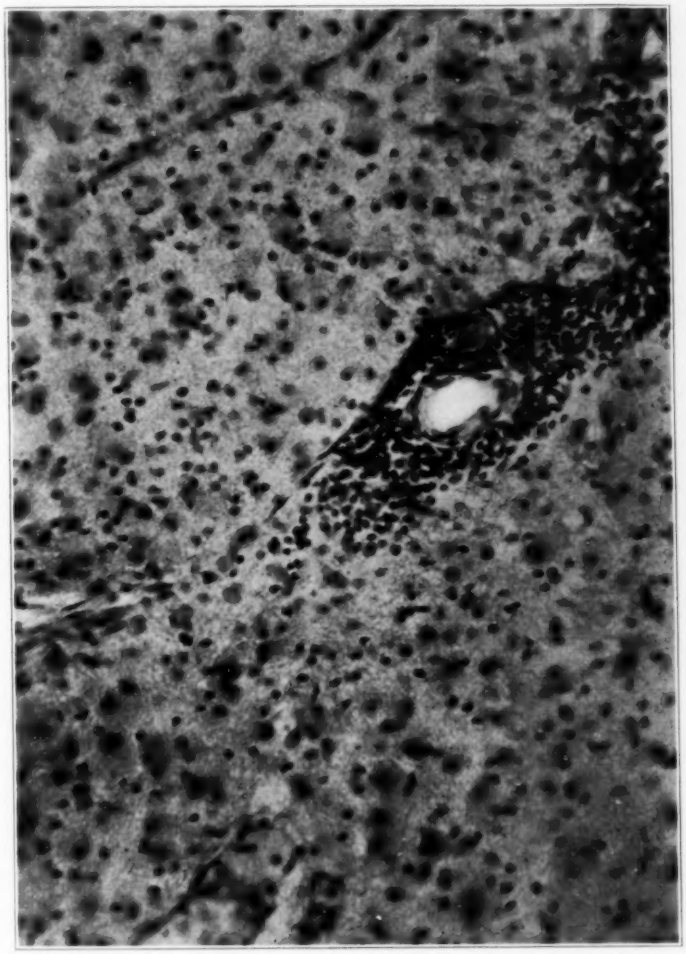


Fig. 13 (case 10).—Section adjacent to foci of softening, showing marked rarefaction, cytoplasmic glia and perivascular infiltration. Toluidine blue stain; high power magnification.

granules within a delicate stroma of collagen fibers, fibroblasts and blood vessels. The adjacent brain tissue was markedly rarefied. The ganglion cells were greatly altered, shrunken, sclerosed or completely destroyed; there were numerous glia nuclei (oligodendroglia), rod cells and especially cytoplasmic glia cells (fig. 13). In some instances the glia cells formed clusters or small nodules. In these areas

the blood vessels were congested and filled with polymorphonuclear leukocytes and lymphocytes. Their walls appeared thickened and had a hyaline appearance. Others exhibited perivascular lymphocytic infiltrations.

More recent minute foci of softening were found in the pons and medulla along the course of the pyramidal tract (left). These foci were more or less edematous, and contained an increased number of glia nuclei, many gitter cells and some cytoplasmic glia cells. The olivary bodies (medulla) contained an unusual number of glia nuclei and rod cells. The vascular changes, as mentioned, consisted in a marked thickening of the vessel walls, which appeared homogeneous, hyaline and sclerotic. Their nuclei stained badly and were scarce. Some vessels were thrombosed; the lumina were markedly narrowed, and the walls were mildly infiltrated (occipital lobe and cornu ammonis). The adjacent parenchyma was pale; its ganglion cells were diminished in numbers and greatly degenerated.

The substance of the brain that was not directly affected was more or less rarefied. It contained an increase of microglia cells and of oligodendroglia, the latter of which were often swollen. The capillaries were prominent, with hypertrophied and proliferated endothelium. Some of the vessels in the white substance were surrounded by macrophages laden with pigment granules.

Some parts of the pia-arachnoid were thickened and hyperplastic, with many mesothelial cell nests. Other portions contained a moderate number of lymphocytes, polyblasts and fibroblasts. In some places the pial meshes were greatly distended and contained numerous macrophages and gitter cells. The pial vessels were congested; some were sclerosed and hyaline in appearance; some were thrombosed.

CASE 11.—*Syphilitic aortitis; headaches and vertigo for several months; paresis of left side of face and left arm; dyspnea; marked weakness; secondary anemia; septic type of fever; death five months later from malignant endocarditis; numerous areas of softening in the brain; many perivascular nodules; resemblance to changes of septicemia.*

History.—A colored man, aged 43, first entered the Cook County Hospital on Feb. 14, 1930, with a history of a chancre twenty years previous to admission; throbbing headache and vertigo of several months' duration; paresis of the left lower part of the face, and paralysis of the left upper extremity for the past three days, and an aortic disease. The patient left the hospital two weeks later in an improved condition. Four weeks later, he returned feeling much worse, complaining of dyspnea on exertion and marked weakness.

Examination and Course.—There was marked visible pulsation of the vessels of the neck. The right pupil reacted sluggishly to light. The heart was enlarged, and double murmurs were heard over the aorta. There were a water-hammer pulse and a capillary pulsation. The deep reflexes in the upper extremities were increased, with paralysis of the left upper extremity. The urine was normal. The hemoglobin was 45 per cent; the red cells numbered 2,100,000, and the white cells, 16,500. The Widal and Wassermann tests were negative. The formaldehyde gel test gave positive results for bacterial endocarditis. Cultures of the blood revealed a small, chain diplococcus. Roentgenograms showed a widened aortic arch. Petechiae developed in the left conjunctiva, and new ones appeared in large numbers during the course of the disease. The temperature was irregular and of a septic type, ranging from 98 to 103 F., and the pulse rate was from 76 to 120 per minute. The patient died on July 21.

Necropsy (Dr. R. H. Jaffé).—The following anatomic diagnosis was made: thrombo-endocarditis of the aortic and mitral valves, with formation of a per-

forated aneurysm in the anterior cusp of the mitralis; insufficiency of the aortic valve; eccentric hypertrophy of the heart and severe parenchymatous degeneration of the myocardium; syphilitic aortitis and moderate atheroma of the aorta; subacute tumor of the spleen, with old and recent partly suppurative infarcts; cloudy swelling of the kidneys and liver; old anemic infarct of the right kidney; edema of the suprarenal cortex, and embolic encephalomalacia.

Brain: There were a few sclerotic plaques in the middle cerebral artery, which was filled by a laminated thrombus. In the posterior part of the right middle frontal convolution a light yellowish-gray area of softening, 20 by 15 mm. in size, was present; there was another one in the midportion of the right anterior central convolution, measuring 5 mm., and a third, 40 by 20 mm. in extent, near the pole of the right temporal lobe.

Microscopic Examination.—The outstanding lesions were areas of softening and nodules. Some areas were extensive and diffuse, and they involved both the cortex and the white substance. In others, they were more or less circumscribed, forming distinct foci. The brain tissue was replaced by dense collections of gitter cells, intermingled with pigment-laden macrophages, fibroblasts, occasional polymorphonuclear leukocytes and numerous blood vessels. The latter, because of their dilated perivascular spaces, appeared as islands in a loose reticulated structure filled with gitter cells. Many vessels showed walls greatly thickened and in a state of hyaline degeneration. The areas adjacent to the softened places were markedly rarefied. The ganglion cells were degenerated and the glia nuclei (oligodendroglia) increased and mixed with many cytoplasmic and microglia cells. The structure of the multiple foci was similar to that described in case 8. The foci were scattered mainly in the cortex. They contained hypertrophied capillaries with markedly proliferated endothelium, surrounded by microglia cells, branched cytoplasmic glia cells and a few gitter cells.

In contrast to the numerous foci of softening, nodules were not numerous. They were of the perivascular type and were situated around the smaller cortical vessels.

The meninges were hyperplastic in spots; in some areas the meshes were greatly distended and edematous, with collections of mononuclear cells around congested blood vessels. Macrophages laden with pigment granules and gitter cells were scattered here and there within their meshes.

CASE 12.—*Rheumatic endocarditis; three months later, a septic type of fever and bronchopneumonia and pericardial effusion; death two months later; multiple foci of softening; severe degeneration of ganglion cells; little or no neuronophagia; severe glial reaction with glial nodules, especially in the pons, medulla and spinal cord; severe meningeal changes.*

History.—A colored boy, aged 8, who was admitted to the Research and Educational Hospitals of the University of Illinois on Dec 12, 1929, had become sick ten days previously with coryza, cough and chilliness. Five days later, the child complained of headaches, respiratory difficulties and pains in both shoulders and neck; the temperature rose to 103 F. On April 29, the patient sustained an injury of the head which was followed by unconsciousness for two days; after this he became mentally dull and less alert. Beginning in July, he had several attacks of "rheumatism," with involvement of the right knee, left ankle and right elbow. Each attack lasted three weeks.

Examination and Course.—There was a systolic murmur over the precordium which was transmitted throughout the entire chest and to the vessels of the neck. The hemoglobin was 55 per cent; the red cells numbered 3,660,000, and the leukocytes 12,500. Urinalysis showed a trace of albumin, with occasional granular and hyaline casts. A culture of the blood was sterile, and the Kahn test was negative.

On December 14, there developed signs of bronchopneumonia on the right side, and on December 19, signs of pericardial effusion which decreased in a few days. There were râles in the right lung most of the time. The size of the area of dulness in the heart varied. A diastolic murmur was heard during the latter half of January. The temperature became of a septic type. Death occurred on Feb. 15, 1930.

Necropsy (Dr. G. Milles).—The following anatomic diagnosis was made: rheumatic pericarditis and endocarditis of the mitral, aortic and tricuspid valves; effusion into the pleural cavities; infarcts of the lungs and spleen; cloudy swelling of the kidneys and passive congestion of the liver. There was no evidence of fracture of the skull.

Brain: The dura was rather thick and slightly injected. The pia was hemorrhagic over the occipital area at the base. Over the basal surface of the frontal and temporal lobes on the right side were brown-stained areas, varying in size up to 1 cm., single or diffuse, from which the gray substance had been entirely denuded. There were two similar areas on the basal surface of the left frontal lobe.

Microscopic Examination.—There were multiple foci of softening, recent and old, which were present in the cortex as well as in the white substance. Gitter cells laden with lipoids (scarlet red stain) and macrophages containing granules of pigment formed the majority of the cells in some foci. Others were made up of dense collections of glia nuclei, rod cells (microglia), fibroblasts, macrophages and gitter cells, which were scattered among a number of hyperemic vessels and capillaries. Acute and severe changes in the ganglion cells were especially striking in this case. In the changes—chromatolysis, vacuolation and perinuclear liquefaction—they resembled the so-called toxic encephalitis. In some areas the ganglion cells were sclerosed and incrusted with lime salts. Edema and rarefaction of the parenchyma were marked. The blood vessels and capillaries were hyperemic and proliferated. The glia often formed clusters or appeared as stellate and syncytial formations (pons, medulla and cervical cord). Rod cells and glia nuclei, in considerable numbers, were occasionally seen around some of the cortical vessels, which were thickened and proliferated. Such foci much resembled minute nodules in the process of formation.

The meninges were more or less thickened and in some places hemorrhagic; their meshes contained a small number of cells, mostly lymphocytes, many mesothelial cells, macrophages, gitter cells and a few polymorphonuclear leukocytes.

CASE 13.—*Night sweats, cough and loss of weight for seven months; left hemiplegia; death three weeks later from malignant endocarditis; positive tests for syphilis in the spinal fluid; combination of all the lesions described in preceding cases; nodules containing giant cells; encapsulated abscess in cerebellum; miliary abscesses; marked vascular lesions resembling miliary aneurysms.*

History.—A white woman, aged 43, was admitted to the Cook County Hospital on July 7, 1930, and died on August 2. Her complaints were night sweats, cough and loss of weight for seven months, and paralysis of the left side of the body, which developed suddenly on the night before admission.

Examination and Course.—The patient was emaciated and stuporous. The face, arm and leg on the left side were weaker than on the right. The pupils reacted sluggishly to light. A questionable Babinski sign was present on the left. The neck was rigid and painful; there was a blowing systolic and low rumbling presystolic murmur at the apex and a heaving apex impulse. The urine contained albumin but no casts. The leukocyte count was 14,000. The Wassermann and the

gel tests were positive. The spinal fluid pressure was decreased; the Pandy test was 2 plus, and the cell count was 292 per cubic millimeter.

The temperature was irregular, ranging from 99.4 to 103 F., reaching 105 F. before death. The pulse rate ranged from 98 to 120 per minute. Petechiae developed over the trunk and the conjunctival and oral mucosa.

Necropsy (Dr. R. H. Jaffé).—The following anatomic diagnosis was made: thrombo-endocarditis of the mitral and aortic valves and of the left auricular endo-

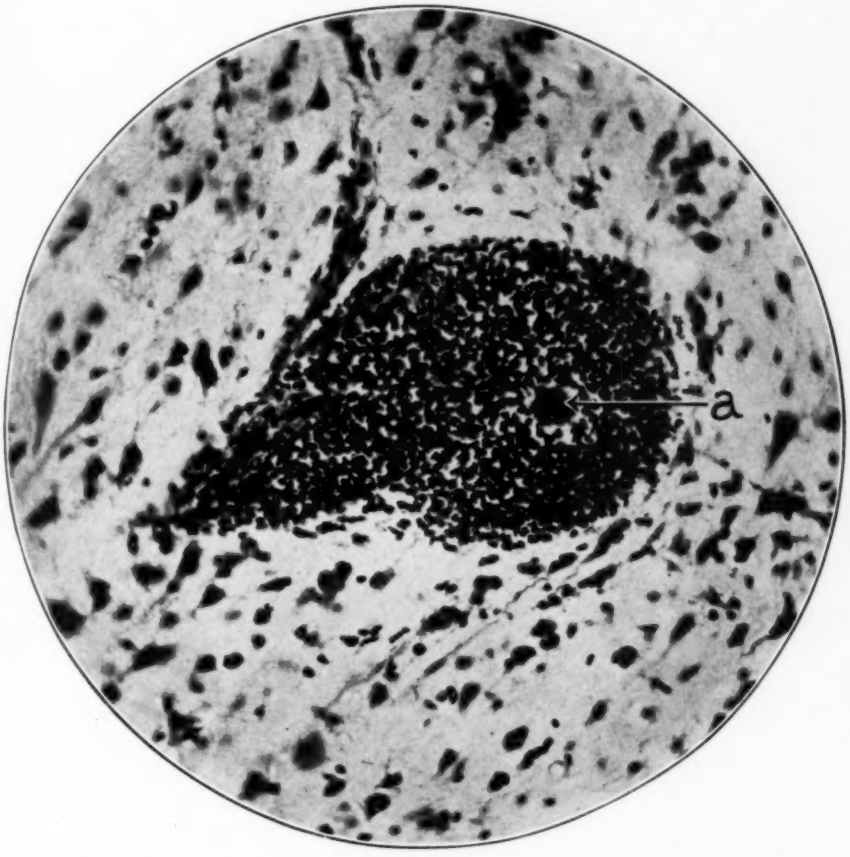


Fig. 14 (case 13).—Motor cortex. Leukocytic nodule; (*a*) clumps of microorganisms. Toluidine blue stain; × 220.

cardium; hemorrhagic infarcts in both lungs; anemic infarcts in the spleen and kidneys; focal glomerulonephritis and interstitial suppurative nephritis; passive congestion and fatty changes of the liver; fibrinous pleuritis of both sides; parenchymatous degeneration of the myocardium and dilatation of all cardiac chambers; cyanotic induration of the spleen, and emaciation.

Brain: The convolutions were flattened; the meninges showed a moderate increase of fluid. The right central ganglia were almost completely liquefied and transformed into a cavity measuring 3 by 15 by 20 mm. The left middle cerebral

artery (at the level of the origin of the lenticulostriate artery) was completely occluded by a firmly organized laminated thrombus. On the inferior aspect of the left cerebellar hemisphere was a longitudinal focus of softening 15 by 6 mm. in area. The left posterior inferior cerebellar artery was occluded by a thrombus. The left flocculus was yellow and softened. The centrum semiovale was flecked by light red areas the size of a pinpoint.

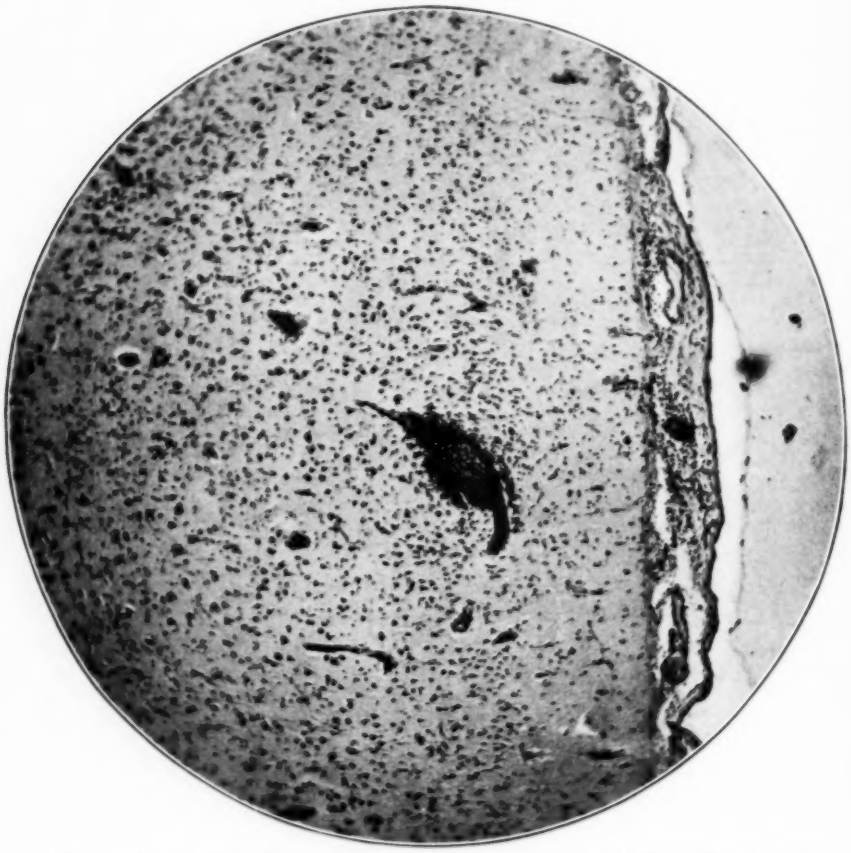


Fig. 15 (case 13).—Motor cortex; small vessel greatly infiltrated and resembling an aneurysm (ballooned). Toluidine blue stain; low power magnification.

Microscopic Examination.—The following were the principal lesions: nodules, large and small foci of softening and abscesses.

In none of the previous cases were the nodules so numerous and of such great variety. They were present in every part of the brain. The most frequent were of the mixed cell type (glia cells, polymorphonuclear leukocytes, lymphocytes and adventitial cells). The next in frequency were the leukocytic nodules and those that resembled miliary abscesses. They usually contained clumps of micro-organisms (fig. 14). Others contained, in addition, an admixture of macrophages. Some of the latter were of glial origin. Glial nodules were not uncommon. Some may

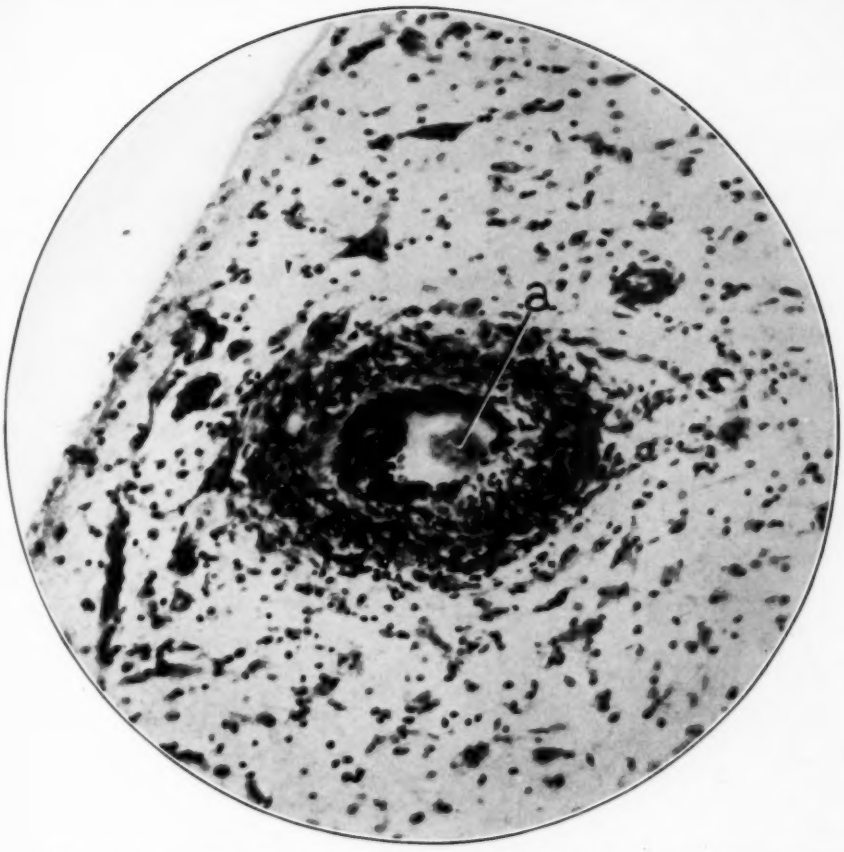


Fig. 16 (case 13).—Substantia nigra; nodule with a giant cell in the center; (*a*) clusters of degenerated micro-organisms. Toluidine blue stain; × 440.

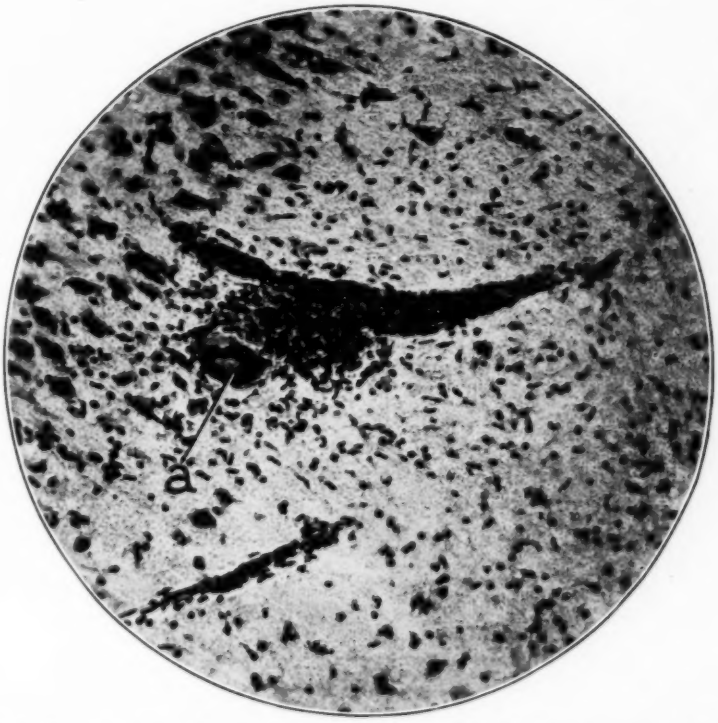


Fig. 17 (case 13).—Cornu ammonis; nodule with infiltrated vessel and giant cell at (*a*) outer pole of nodule. van Gieson stain; low power magnification.

be classified as vascular. The vessels were dilated and greatly infiltrated with polymorphonuclear leukocytes that resembled miliary dissecting aneurysms (fig. 15). A rare and unusual type was the giant cell nodule. As shown in figure 16, the center of the nodule consisted of a large giant cell, with many oval vesicular nuclei gathered around the periphery of the cell body. The latter contained a dustlike mass-remnant of degenerated micro-organisms. This type of nodule much resembled a tubercle, and was found in the region of the substantia nigra. In

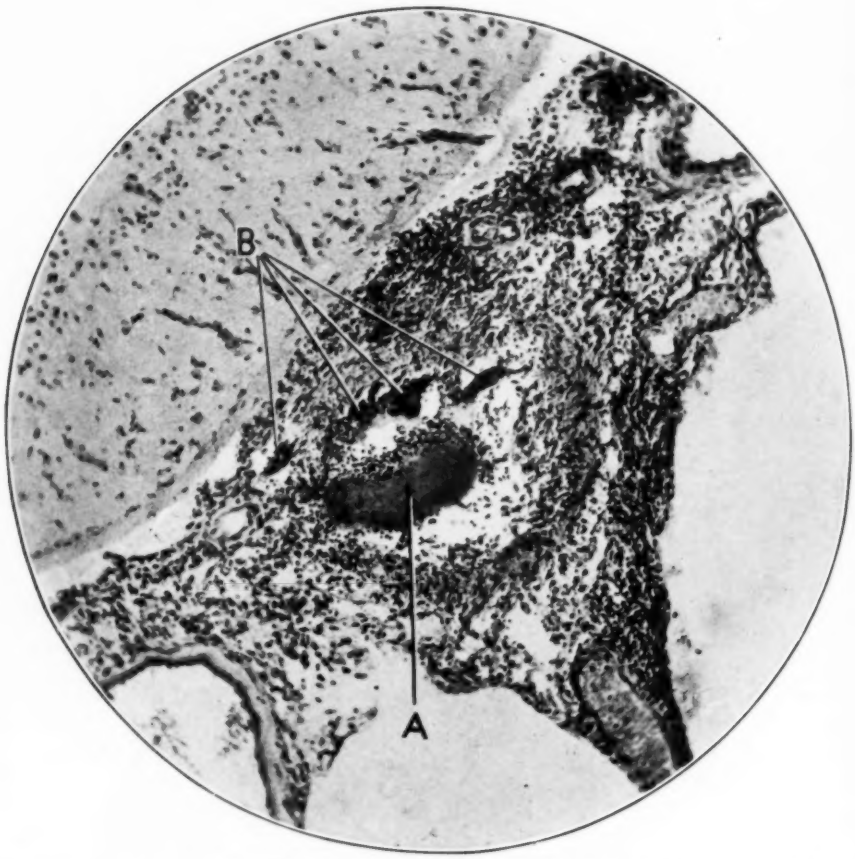


Fig. 18 (case 13).—Pia-arachnoid markedly infiltrated with various cells as described in the text. (*A*) large clump or mass of micro-organisms more or less degenerated, invaded and surrounded by leukocytes and giant cells; (*B*) giant cells. Toluidine blue stain; × 110.

others the giant cells were much smaller and were situated at the periphery of the nodule. In others, again, single giant cells were found either isolated at one pole of the nodule or within them (fig. 17).

The minute and large foci of softening were similar to those previously described. Frequently one could find in the same section nodules, small and large softenings, many gitter cells, foci of necrosis and miliary abscesses intermingled with clumps of bacteria.

An isolated abscess was present in the cerebellum. It measured 3.5 mm. in diameter and was encapsulated. It consisted of an aggregation of leukocytic nodules or foci, many of which contained in their centers clumps of micro-organisms that were more or less destroyed. The center of the abscess was not liquefied, but was necrotic.

The other changes were similar to those described in the previous cases but were more marked. There were cerebral edema, with extensive areas of rarefaction, acute and severe ganglion cell changes and neuronophagia with diffuse proliferation of glia. The vessels were congested, hypertrophied and proliferated; many exhibited perivascular infiltrations, and those adjacent to foci of softening contained thrombi with hyaline degeneration of the walls.

The meninges were greatly thickened and hyperplastic. The meshes were much infiltrated with numerous lymphocytes, polyblasts and fibroblasts. Some areas contained clusters of polymorphonuclear leukocytes and macrophages, and occasionally gitter cells. The vessels were usually congested; some were filled with leukocytes and bacteria. Here, also, many giant cells surrounded large masses of micro-organisms, some of which were more or less destroyed (fig. 18). Giant cells were also found in the meninges of the cerebellum, which formed part of the capsule around the abscess already described.

COMMENT

Cerebral lesions in malignant endocarditis are extremely common. Of the consecutive series of thirteen fatal cases reported, all showed pathologic lesions in the brain even when, as in cases 1, 2 and 4, definite clinical manifestations other than those usually regarded as of septic origin were absent. In some cases, however, the cerebral symptoms dominated the clinical picture (cases 5, 6 and 13).

The types of lesion in the brain may be as varied as the clinical picture. They may be inflammatory or degenerative, circumscribed or diffuse, and the forms are frequently combined. Indeed, the lesions of the brain are only a partial manifestation of a general involvement of the central nervous system and of the whole body. They represent reactions of the nerve tissue to the infectious process that underlies malignant endocarditis. Bacteremia is usually present and is of especial interest in regard to its effect on the nerve tissue. Micro-organisms and septic emboli from the thrombo-ulcerative valves of the heart more or less flood the blood stream and become lodged in various organs, including the brain. While every case shows a combination of different types of reaction, for purposes of description they may be grouped under the following descriptive titles:

CIRCUMSCRIBED LESIONS

Though circumscribed, the lesions are multiple and are scattered diffusely through the brain. They may be grouped as: (1) nodules, (2) abscesses, (3) vascular lesions, (4) degenerative lesions and (5) attempts at repair.

1. *Nodules.*—These collections of cells vary in size and shape and in their cellular content; they may be considered as defense reactions against the invading micro-organisms. They have the same significance as the nodules in trichinosis encephalitis [1] and in some infections with Staphylococcus pyogenes-aureus.[2] In the former they harbor the trichina embryos, and in the latter staphylococci are invariably present in the nodules, either free or within cells. Some of the cases here reported were typical of a streptococcus infection. Damage to the blood vessels by streptococci may also cause reaction of the glia and mesodermal tissues and give rise to the formation of nodules. The micro-organisms may be destroyed early by the proliferated cells and consequently be absent when the nodule is studied (cases 1, 2, 3 and 4). However, when the cocci were present in large numbers, the nodules were invariably of a mixed cell type (cases 5, 6, 7 and 13). Besides glia cells, they contained polymorphonuclear leukocytes, lymphocytes and macrophages as an additional cellular reaction. When the brain is flooded with bacterial emboli, the reactions may include nodules that are chiefly leukocytic or miliary abscesses.

The types of nodules encountered in the cases here reported, designated according to the predominating form of cell of which they were composed, were as follows:

(*a*) Glial: In this type the glial elements formed the principal cells of the nodules (case 1, figs. 1 and 2). These were the outstanding lesions in case 1. They were situated around the capillaries and mainly present in the white substance, basal ganglia, pons, medulla and, in one instance, also in the cervical cord (case 12).

(*b*) Glial-Mesodermal: In addition to glia cells, an admixture of mesodermal elements was present, mainly proliferated adventitial cells, a few lymphocytes and an occasional polymorphonuclear leukocyte. This type was the most frequent. They were situated about blood vessels of medium or smaller size and are illustrated in figures 3 and 4 (cases 2, 3, 4 and 13).

(*c*) Mesodermal or Perivascular: The cell collections were mainly mesodermal. These were present about medium-sized cortical vessels (fig. 5, cases 3, 4, 11 and 13). The infiltrating and proliferating cells were confined or limited to the blood vessels and their perivascular spaces. The cells were mainly adventitial cells, with some lymphocytes. They differed from perivascular lymphocytic infiltration in their slow formation. The vessels were usually empty, devoid of blood and at

1. Hassin, G. B., and Diamond, I. B.: Trichinosis Encephalitis, Arch. Neurol. & Psychiat. **15**:34 (Jan.) 1926.

2. Diamond, I. B.: Changes in the Brain in Pyemia and Septicemia, Arch. Neurol. & Psychiat. **20**:524 (Sept.) 1928.

times difficult to recognize. In some instances, the cells were collected laterally at one pole of the vessel wall and occasionally, in addition, contained an isolated multinuclear giant cell (cases 3 and 4). Secondary diffuse reaction on the part of the glia (fig. 10, case 5) may take place when the vessel finally breaks down (acute exacerbation).

(*d*) Glial-Leukocytic: An equal number of glia cells and polymorphonuclear leukocytes were present. These nodules always harbored micro-organisms. They also were situated about the blood vessels. The walls of the latter were usually infiltrated with polymorphonuclear leukocytes, and at times were ruptured with slight hemorrhages intermingled with macrophages (fig. 8, cases 5, 6, 7 and 13).

(*e*) Leukocytic or Miliary Abscesses: The cells were exclusively polymorphonuclear leukocytes. These usually contained central clumps of micro-organisms (cocci), which in many instances were degenerated and the leukocytes necrotic, with the histologic picture of miliary abscesses (fig. 14, cases 5, 6 and 13). The occurrence of leukocytic nodules or miliary abscesses was first mentioned by Huguenin [3] and later by von Leichtenstern,[4] Lemke,[5] Flater [6] and Kimmelstiel,[7] who also described glial and glial-mesodermal nodules in infections with Streptococcus viridans.

(*f*) Nodules Containing Giant Cells: As the infective process is usually subacute (endocarditis lenta), the tissue reaction leads occasionally to the formation of giant cells as an additional defense which operates by walling off and destroying the morbid agent.

In cases 3 and 4 an occasional giant cell was present in the mesodermal nodule, but in case 13 giant cells were numerous. They were situated around as well as within the nodules. Occasionally they were of large size and occupied the center of the nodules, contained a great number of vesicular oval nuclei gathered in clumps around the periphery of the cell body, and surrounded masses of degenerated micro-organisms (fig. 16, case 13). The giant cells in turn were encircled by large numbers of glial and mesodermal elements; the whole much resembled a tubercle. In others, giant cells were situated and scattered around the periphery of the nodules. The latter also contained in their centers clumps of bacteria, which were surrounded by polymorphonuclear leukocytes, mesodermal cells and glia cells. In others, again, single multinuclear giant cells were found isolated at one pole of the nodules (fig.

3. Huguenin, in Ziemsen: Handbuch der speciellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1878, vol. 11, p. 738.

4. von Leichtenstern, O.: Deutsche med. Wchnschr. **18**:93, 1892.

5. Lemke, R.: Arterienveränderungen bei Infektionserkrankungen, Virchows Arch. f. path. Anat. **243**:53, 1923.

6. Flater, A. B.: Endokarditis und Gehirn, Klin. Wchnschr. **32**:2094, 1924.

7. Kimmelstiel, Paul: Ueber Viridans-Encephalitis bei Endocarditis lenta, Beitr. z. path. Anat. u. z. allg. Path. **79**:39, 1927.

17, case 13). The giant cells were derived most likely from the proliferated cells of the vessels, although a few resembled glia cells that appeared to have fused and formed a syncytium.

2. *Abscesses.*—The abscesses were usually of the miliary type already described as leukocytic nodules, and were sometimes numerous (cases 5, 6 and 13). Occasionally, a number of them may become fused and transformed into a larger abscess which is encapsulated, as in case 13. The giant cells scattered in the capsule assisted in the walling-off process. Similarly, in the pia-arachnoid giant cells surrounded large masses of degenerated micro-organisms and polymorphonuclear leukocytes (fig. 18, case 13).

3. *Vascular Lesions.*—The blood vessels were usually greatly changed; their layers were proliferated and sometimes infiltrated throughout with leukocytes—a panarteritis (cases 5 and 13, fig. 15). Aside from the proliferative and infiltrative phenomena, the vessels may also show degenerative changes (cases 2, 4, 10, 11 and 13). Vascular lesions resulting from streptococcic endocarditis were emphasized by Schottmüller [8] and Siegmund,[9] who laid stress on the formation of aneurysms. These lesions were observed in my material only in case 13. Winkelman and Eckel [10] found a uniform productive (toxic) endarteritis. On the other hand, Istomanowa [11] found in thirty cases only a few changes in the vessels, and these were due to occlusions of the larger cerebral vessels by emboli.

4. *Degenerative Lesions.*—These consisted of softening and necrosis. As a result of the vascular lesions, embolism and toxemia, focal softenings and necrosis are frequent. They may be: (*a*) minute (cases 2, 3, 4, 7, 8, 9 and 11) or, when associated with severe vascular changes, (*b*) large (cases 10, 11, 12 and 13). Small hemorrhages (cases 5 and 7) and abscesses (case 13) may be associated with them.

(*a*) Minute Foci of Softening: These are usually multiple and often described as partial softening and "Verödungsherde." They are characterized by light areas that contain a number of markedly prominent and proliferated capillaries (fig. 11, case 8). The affected brain tissue may be loosened or necrotic and replaced by a number of proliferated glia cells, many elongated and with branched processes (microglia), and a few gitter cells. The endothelial cells of the capil-

8. Schottmüller, N.: Endocarditis lenta, München. med. Wchnschr. **57**:617, 1910.

9. Siegmund, H.: Veränderungen der Gefässwände und des Endokardiums bei Scharlach, Centralbl. f. allg. Path. u. path. Anat. **44**:314, 1928.

10. Winkelman, N. W., and Eckel, J. L.: The Brain in Bacterial Endocarditis, Arch. Neurol. & Psychiat. **23**:1161 (June) 1930.

11. Istomanowa, T.: Histologische Befunde bei Endokarditis lenta, Virchows Arch. f. path. Anat. **268**:225, 1928.

laries are greatly swollen and often exhibit mitotic figures. These foci were especially marked in case 8, and less so in cases 2, 3, 4, 9 and 11.

(*b*) Complete Softening: These were the principal lesions in cases 10, 11 and 12, and in cases 7 and 13 in addition to other lesions or changes. They are more or less large, and the brain tissue is completely replaced by a great number of gitter cells, some of large size, and phagocytes laden with granules in a delicate stroma of collagen fibers, fibroblasts and blood vessels (fig. 12, case 10). The brain tissue adjacent to such foci may be markedly rarefied and contain a great number of Hortega cells and cytoplasmic glia cells (fig. 13, case 10).

Foci of Necrosis with no Reactive Phenomena: These were especially marked in case 2, and were less in cases 4 and 10. The capillaries and smaller vessels (caudate nucleus, white substance and optic thalamus) were completely obstructed by masses of cocci which evidently multiplied before or soon after death. Both the vessels and the surrounding tissue stained poorly or not at all. The tissue was edematous and necrotic. The ganglion cells appeared as shadows. Occasionally a few pyknotic glia nuclei stained deeply.

Foci of Necrosis with Reactive Leukocytic Infiltrations: In cases 3 and 13, the foci were infiltrated with many polymorphonuclear leukocytes (fig. 7, case 3). These were evidently secondary to small emboli, as some of the larger vessels were completely blocked by darkly stained cellular débris. The smaller vessels and capillaries in the necrotic area were prominent and densely infiltrated, and their lumina were packed with polymorphonuclear leukocytes. Many of the latter formed collections that much resembled miliary abscesses. The cells were markedly pyknotic or broken up as nuclear fragments, free or within macrophages. Micro-organisms were absent. The few ganglion cells present stained poorly and appeared as shadows. Gitter cells were few. A glial reaction was marked around the necrotic foci, as evidenced by an increase in glia nuclei (oligodendroglia), microglia and cytoplasmic glia.

5. *Attempts at Repair.*—In cases 3, 4, 8, 11 and 13, a number of the foci of softening were in the process of organization or healing. These foci resembled somewhat the nodules, but were larger in size and more irregular in shape (fig. 6, case 3). Their structure and cellular content varied. They contained numerous capillaries, many of which were newly formed and were scattered in richly cellular areas. The majority of the cells were glia and microglia, with many gitter cells and macrophages laden with pigment granules.

DIFFUSE REACTIONS

The diffuse changes are parenchymatous, vascular and meningeal, and are typical of a meningo-encephalitis (cases 5, 6 and 7). In cases 5 and 6 there were, in addition to the focal, diffuse infiltrations of the

parenchyma with polymorphonuclear leukocytes, marked congestion of the vessels and perivascular lymphocytic infiltration (figs. 8 and 10, case 5). The glia also was markedly proliferated. Frequently, polymorphonuclear leukocytes invaded the proliferated glial elements, giving them the appearance of macrophages (fig. 9). The latter often formed clusters, mixed with leukocytes, about infiltrated and proliferated blood vessels. The parenchyma was edematous, and the ganglion cells exhibited marked degenerative changes with neuronophagia. In case 7 the encephalitis was of the so-called hemorrhagic type; minute hemorrhages, focal and diffuse, dominated the histologic picture. It differed from cases 5 and 6 by fewer and milder leukocytic infiltrations and by fewer glial-leukocytic nodules. In cases 9 and 12, the changes, especially those in the ganglion cells, were not unlike those described in so-called acute toxic encephalitis,[12] namely, marked chromatolysis, vacuolation and perinuclear liquefaction. Clinically, case 9 was of acute course with death in seven days. Associated with the ganglion cell changes there was proliferation of the glia, blood vessels and meninges. Case 12 is of interest in that the endocarditis was of the rheumatic type. The ganglion cells were severely degenerated, with little or no neuronophagia, associated with multiple foci of softening and severe meningeal changes.

Cases complicated by meningo-encephalitis have been reported by Wohlwill,[13] Kimmelstiel[7] and Zalatowa.[14] Aside from the typical nodules, the changes found in the brain as complications of endocarditis are those described in pyemia and septicemia.[15]

CONCLUSIONS

1. Changes of the brain are frequent in malignant endocarditis.
2. They are both circumscribed and diffuse.
3. The circumscribed lesions are usually in the form of nodules.
4. The diffuse lesions are in the form of a meningo-encephalitis.
5. Both are manifestations of a defense reaction against an infection and intoxication.
6. The latter is responsible for the degenerative changes.
7. Other changes (softening and necrosis) are secondary, the result of vascular embolism or thrombosis.

---

12. Low, A. A.: Acute Toxic (Nonsuppurative) Encephalitis in Children, Arch. Neurol. & Psychiat. **23**:696 (April) 1930.

13. Wohlwill, F. B.: Ueber mykotische Encephalitis, Arch. f. Psychiat. **79**:577, 1927.

14. Zalatowa, N. A.: Gehirnveränderungen bei Endokarditis, Virchows Arch. f. path. Anat. **277**:420, 1930.

15. Diamond (footnote 2). Weimann, W.: Gehirnbefunde bei septischer Allgemein-Infektion (nach kriminellen Abort), Ztschr. f. d. ges. Neurol. u. Psychiat. **114**:242, 1928.

TOXIC ENCEPHALOPATHY IN MEASLES

ARMANDO FERRARO, M.D.
Research Associate in Neuropathology, New York State Psychiatric Institute and Hospital
AND
I. H. SCHEFFER, M.D.
Deputy Medical Superintendent, Willard Parker Hospital
NEW YORK

Encephalitic complications occurring in measles are well known, and recently their occurrence has been the subject of careful clinical and histologic investigation.[1]

There is a consensus among the various authors as to the histologic picture that characterizes the so-called "measles encephalitis." We ourselves have reported six cases of this condition in which the lesions consisted especially in a perivascular proliferation formed largely by microglial elements. The perivascular proliferation is scattered throughout the cortex and white substance, but involves the latter more severely (fig. 1). Under a low power magnification, the perivascular proliferation gives an impression of a perivascular infiltration, but a careful study of the elements forming the proliferation excludes the existence of hematogenous elements, while the use of appropriate specific stains discloses beyond any doubt the microglial nature of the cells. It is then clearly a proliferation that has nothing in common with the usual infiltration found in other infectious conditions. At times, the proliferation invades a considerable area as a result of the presence of numerous blood vessels surrounded by a more or less pronounced amount of perivascular elements. The proliferation seems to involve more severely the veins, which are engorged and some of which present red thrombi.

From specific stains the elements forming the proliferation appear to be microglia cells (fig. 2), some of which have the elongated appearance of "Stäbchenzellen," while others are being transformed into compound granular corpuscles (fig. 3).

Submitted for publication, April 10, 1931.

From the Department of Neuropathology of the New York State Psychiatric Institute and Hospital and the Willard Parker Hospital.

1. A detailed bibliography on this subject will be found in our previous article: Encephalitis and Encephalomyelitis in Measles; Report of Six Cases, Arch. Neurol. & Psychiat. **25**:748 (April) 1931.

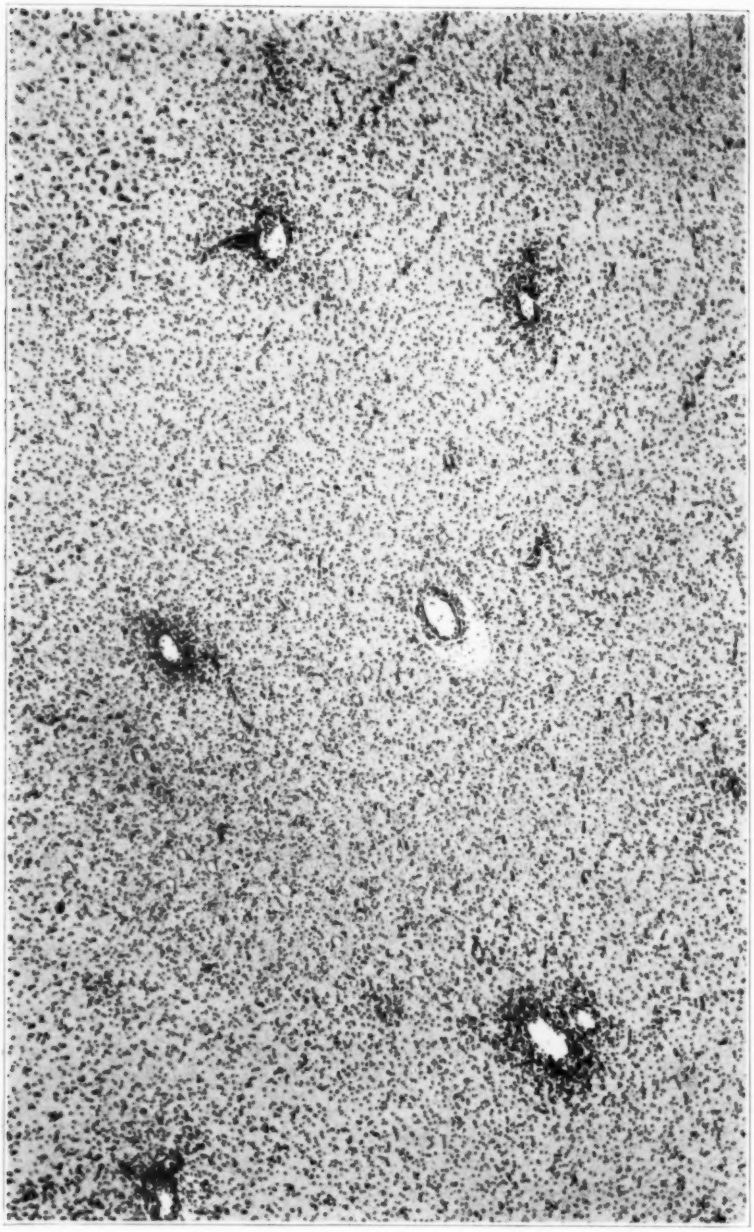


Fig. 1.—Perivascular proliferation in a case of typical measles encephalitis.

Accompanying the perivascular proliferation there is a concomitant process of perivascular demyelinization, which constitutes another characteristic of the pathologic process. Lesions involving axis cylinders are to be expected in the demyelinized areas and have been reported in all our cases.

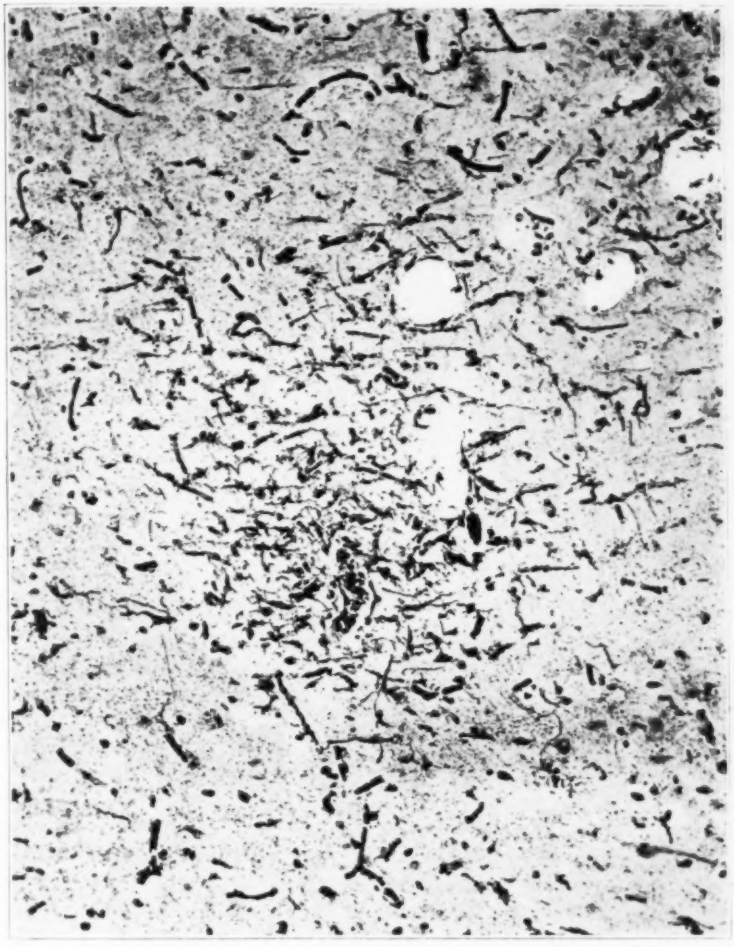


Fig. 2.—Impregnation of the perivascular elements, showing that they are mainly formed by microglia cells; del Rio Hortega silver carbonate method (Globus and Penfield modification).

Less characteristic is the macroglial reaction, with both progressive and regressive manifestations. The nerve cells do not seem to suffer considerably from the process. Large areas are seen in which no evident pathologic change can be detected in the ganglion cells, although in the midst of the areas of proliferation, in the cortex, cells may be

seen undergoing all the stages of degeneration from a simple swelling to a complete disintegration. Here and there, however, irrespective of the presence of perivascular proliferation, areas are encountered where the nerve cells are diffusely involved, showing all stages of the so-called severe type of lesion of Nissl.

Fig. 3.—High power magnification of microglia cells being transformed into fat compound granular corpuscles; del Rio Hortega silver carbonate method.

It is important to point out that the lesions that are found in measles encephalitis are identical with lesions that have been described in vaccine encephalitis (Turnbull and McIntosh, Bastiaanse, Perdrau, Hassin and Geiger, Lucksch, Bouman and Bok, Wiersma, etc.), in influenza encephalitis (J. G. Greenfield, Bassoe and Grinker) and in

rabies vaccine encephalitis (Bassoe and Grinker). The identity of the pathologic process in so many different conditions has created a wide discussion in establishing the mechanism of the production of the lesions described.

There are at present three main views as to the pathogenesis of encephalitis following vaccination of acute exanthematous diseases: (1) that the lesions in the brain and cord are directly due to the action on the nervous system of the virus of smallpox, vaccinia, measles, influenza, etc. (McIntosh and Turnbull, Lucksch, Gorter and Van Nederveen and Bijl); (2) that they represent an allergic or an anaphylactic phenomenon activated by the preceding illness (Glansman, Rivers, Keller), and (3) that they are caused by an unknown virus or toxin which is in some way empowered by the exanthematous disease to attack the nervous system (Levaditi and Nicolau, Pondman, Keller, Pette, Wohlwill, Greenfield, Hassin).

Against the first view is the fact that infection of the brains of rabbits and monkeys with vaccinia produces a very different histologic picture from that of postvaccinal encephalitis. The virus tends to attack the meninges primarily, and according to the work of E. W. Hearst and R. W. Fairbrother, the essential lesion is a fibrinous, hemorrhagic and polymorphonuclear meningitis. There are, besides, alterations in the underlying nerve structures, and they are seen only where the meningitis is most severe and are no doubt due, at any rate in part, to disturbances in nutrition consequent on this and on compression resulting from the intense local edema. According to these authors, it is hardly possible to imagine a greater contrast between the picture of vaccinal encephalitis and that seen in the disseminated encephalomyelitis following vaccination.

Contrasting with this presentation is the one of J. McIntosh and W. Scarff, who claimed that virulent strains of vaccinia can produce in rabbits a definite meningo-encephalitis after intracerebral, intravenous and intradermic inoculations. The lesions produced are directly comparable with the visceral lesions in rabies and with those in postvaccinal and postvariolar encephalitis in man.

With contrasting results of this nature, the wisest thing to do is to wait for confirmatory work in favor of either one of the reports before deciding against or in favor of the identity of natural and experimental encephalitis. Nevertheless, the negative results of Hearst and Fairbrother do not allow us to accept, for the present at least, the first hypothesis in discussion.

The hypothesis of an anaphylactic phenomenon is supported, according to Greenfield, by the case of transitory paraplegia following antirabic treatment and by fatal cases of this kind in which Babes and

Marinesco found a condition closely resembling acute disseminated myelitis. But if the condition is due to an anaphylactic response, one expects it to be discovered in some of the fatal cases of tetanus or of diphtheria following the injection of antitoxin serum. It is, of course, conceivable that some kind of reaction occurs in virus infections which might loosely be called anaphylactic, but which is different from an anaphylaxis due to foreign protein (Greenfield).

Conversely, the third hypothesis that the condition is caused by an unknown virus or toxin is to some extent supported by instances of encephalitis or myelitis of the same nature following vaccination, smallpox, measles, rabies and influenza. According to Greenfield, there is no doubt that all these forms have occurred much more frequently during the past few years than at any period since the beginning of the present century, but the pathologic records of Westphal and Barlow and Penrose indicate that the cases are not those of a new disease; that from the clinical side similar nervous complications were known after smallpox one century ago and after measles two centuries ago. While an alteration of the virus of vaccinia so that it acquires a special virulence for the nervous system is conceivable, it is highly improbable that a similar alteration would, during certain years, also affect the virus of measles and that of influenza. In the opinion of Bassoe and Grinker, who minimized the ability of the neuropathologist to determine the toxic, bacterial or virus origin of any disease, possibly a whole group of different viruses may be responsible and must be searched for in all types of encephalitis without reference to their pathology.

To us, in the present state of knowledge, it seems that acute disseminated encephalomyelitis accompanying measles is most likely a toxic reaction of the central nervous system which may occur in a number of different virus infections. In favor of our conception we are reporting the following two cases of encephalitis accompanying measles in which the histologic picture differs from the usual picture seen in measles encephalitis and definitely points to the toxic nature of the fundamental lesions.

REPORT OF CASES

Case 1.—C. T., a white girl, aged 5, who was admitted to the hospital on May 27, 1930, at 1 p. m., was mentally retarded, constantly soiling her clothing and bed clothes, taking little interest in her surroundings and seldom playing with other children. She had had pertussis. On May 14, varicella developed. There was a history of colitis of uncertain duration. On May 24, in the afternoon, the child showed a fever (temperature 102.2 F.), and a rash appeared on the face. Cough and coryza were present. On the day following, the temperature rose to 104 F., and the rash became more generalized. There was moderate cough. On the morning of May 26, the temperature was 102.4 F.; at noon, 103 F.; at 4 p. m., 102 F. At this time, the patient became dyspneic and had marked pallor. The

pulse rate was from 110 to 120, and was regular. Toward night, the child became progressively drowsy and lapsed into coma.

Physical Examination.—On admission, the patient was moderately well developed and nourished. She was in coma. The respirations were shallow and Cheyne-Stokes in character. Cyanosis was general. There was a faded macular rash on the face and body (presenting the appearance of a measles rash of from four to five days' duration). The child did not respond even to painful stimulation. She gritted her teeth occasionally. No facial palsy was present. The eyelids were tightly closed and resisted opening. The pupils were equal and reacted to light. There was a rolling nystagmus, chiefly horizontal, occasionally vertical. Conjunctivitis was present. The ocular fundi (under atropine mydriasis) showed bilateral papillitis, which was more marked on the right side. There was marked engorgement of the blood vessels. There was a small retinal hemorrhage on the temporal side of the right disk. There was no cervical rigidity. The knee and achilles reflexes were present. The deep reflexes of the upper extremities were not elicited. A bilateral Babinski sign was present; the Oppenheim and Gordon tests were positive. There was no ankle clonus and no Kernig or Brudzinski signs. The patient was incontinent of urine and feces. The drums of both ears were dull gray, but showed no bulging, and there was no discharge. A small amount of dried secretion was present in both nares. There was marked trismus, and the mouth opened with difficulty. The pharynx was full of frothy saliva and mucus. The tongue had a dirty coating. Spots present on the buccal mucosa were suggestive of faded Koplik spots. There was a pigeon breast deformity; there was no impairment of the percussion note over the lungs; the breath sounds were diminished over both bases posteriorly; respirations were shallow; coarse râles and rhonchi were heard throughout. The heart sounds were clear, regular and accelerated; there were no murmurs. The abdomen was soft; no solid viscera were palpable. The extremities were moderately spastic.

On admission, clear cerebrospinal fluid was obtained by lumbar puncture; there was a marked increase in pressure; 35 cc. was removed; there were 40 cells per cubic millimeter, all lymphocytes; sugar was ++. The blood count was: white cells, 20,400; polymorphonuclears, 52 per cent; lymphocytes, 44 per cent; large mononuclears, 4 per cent; hemoglobin, 70 per cent.

Course.—At 7 p. m., the patient began to have generalized myoclonic convulsions at frequent intervals. Her color was cyanotic, and the respirations were shallow. The pulse was rapid and of poor quality. The temperature, which was 104.4 F. on admission, rose steadily, and the child's condition grew rapidly worse. She died at 3:15 a. m. on May 28.

General Autopsy (Dr. Lawrence Smith).—There was no discharge from the ears or nose. There was no appreciable cervical lymphadenopathy. The chest showed a marked rachitic deformation of the chicken breast type. There was slight edema around the epiglottis. The trachea and bronchi showed marked acute injection of the mucosa. The lower third of both lungs showed a diffuse hypostasis with probable beginning consolidation. The hilar and peritracheal nodes showed a corresponding acute lymphadenitis. There was moderate hypertrophy of the lower ileum and cecum, with hyperplasia of the mesenteric nodes, particularly those in the ileocecal angle. The spleen was about twice the normal size, and on section showed striking lymphoid hyperplasia.

On opening the skull, the dura appeared normal except for moderate congestion. It stripped readily, but showed a considerable number of pacchionian bodies. The brain showed a striking degree of congestion, with punctate perivascular hemor-

rhages throughout the white matter, which was most marked in the occipital lobes and around the caudate and lenticular nuclei. There were no focal lesions other than the vascular ones.

Anatomic Diagnosis.—The anatomic diagnosis was: measles; bilateral hypostatic bronchopneumonia; acute catarrhal tracheobronchitis; lymphoid hyperplasia of the spleen, mesenteric nodes and gastro-intestinal tract; acute encephalitis.

Histologic Study of the Nervous System.—In the frontal cortex, the meninges were thick, but no inflammatory process was present. The thickness was due to proliferation and hypertrophy of cellular elements consisting of large mononuclear cells of the hystiocyte type and of elongated spindle-shaped cells.

The lamination of the cortex was grossly well preserved, although here and there a reduction of the cellular elements was evident in some layers, being more pronounced in the middle and outer ones. There was a total absence of the perivascular proliferation that characterizes the usual type of measles encephalitis, and the white substance was entirely free from collected elements surrounding the veins.

The characteristic lesion in this case was a diffuse involvement of the nerve cells; it involved all the layers, although at times it predominated in the upper layers. The lesion consisted in a severe swelling of the nerve cells; the cell body appeared swollen and the Nissl substance was completely disintegrated. The result was that the nucleus was surrounded by a clear area, which appeared edematous. The nerve cell assumed a roundish aspect, and the processes were barely seen. Under a higher power, the changes were seen more readily (fig. 4). The nucleus of the nerve cell was at times much better preserved than the cytoplasm; it kept its roundish aspect, and here and there the chromatin content was detectable and the nucleus well identified. All the stages of acute swelling were present, from a beginning chromatolysis to complete disintegration of the cell through the breaking down of the membrane and the gradual fading of the nuclear content. As a result of the destruction of the cells, acellular areas were formed. Some of the nerve cells did not undergo acute swelling but only a gradual process of chromatolysis, leading to the gradual fading of the whole element. Here and there, nerve cells were found which, instead of undergoing the predominant type of liquefaction, underwent the so-called severe type of degeneration of the nerve cell as described by Nissl, a condition in which the cytoplasm disintegrates into small annular formations and the cell gradually breaks down and completely disappears.

In the temporal cortex, the lesions were not so pronounced as in the frontal cortex, but there was an evident diminution of nerve cells with the formation of definite acellular areas. The postcentral gyrus showed the same type of lesion, differing only slightly in intensity.

In the occipital cortex, the lesions were more pronounced than those in the temporal and parietal, and were more comparable in intensity with those in the frontal area. Here, too, the swelling involved all areas and seemed to have a predilection for external ones.

In the caudate nucleus and lenticular nucleus, the acute swelling and liquefaction was diffuse, but involved especially the large cells of the globus pallidus.

In the mesencephalon and pons, the lesions were diffuse and did not seem to have a predilection for any particular area.

The Purkinje cells of the cerebellum had undergone a process of homogenization in which all the chromatin bodies had disappeared, the element having acquired a roundish homogeneous appearance and the nucleus a shrunken aspect.

It is important to note that most of the blood vessels, especially the small ones of the cortex, showed an acute swelling of the endothelium. The condition was so

pronounced as to simulate here and there a condition of endarteritis, but with a higher magnification swelling alone could be detected, and there were no signs of proliferation of the elements. This lesion was important, as it was diffuse and undoubtedly interfered with the blood supply of the areas involved.

With appropriate stains for microglia and oligodendroglia, a diffuse swelling of the latter was detected (fig. 5). The swelling was diffuse and involved both

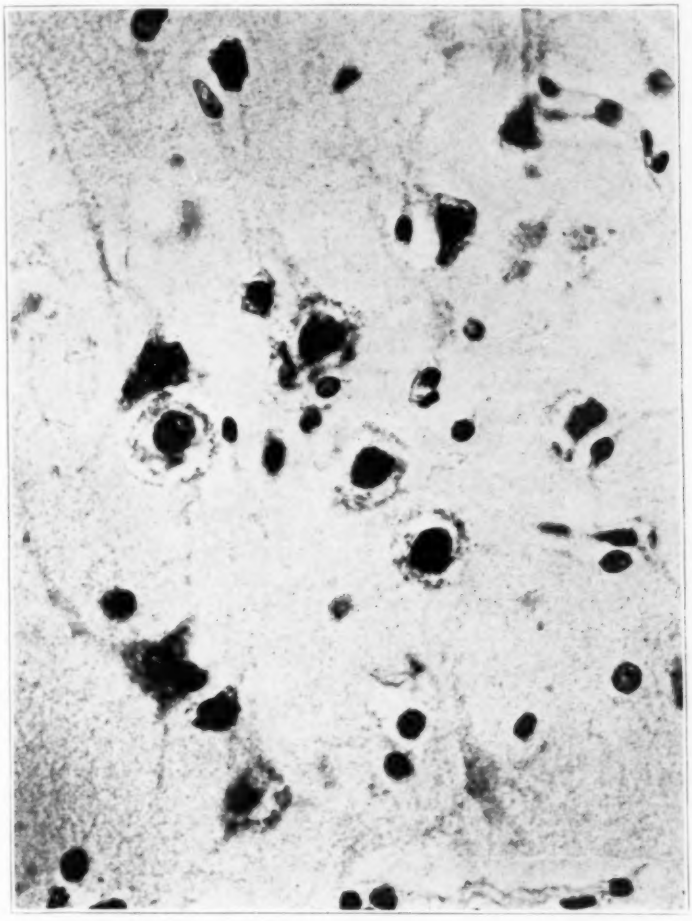


Fig. 4.—High power magnification of nerve cells undergoing an acute process of liquefaction; Nissl stain.

the cortex and the white substance. The microglia were less swollen, but here and there elements were seen undergoing acute degenerative changes. Here and there roundish reticular cells were seen, presumably a stage of a rapid transformation of microglia into compound granular corpuscles.

The astrocytes underwent both progressive and regressive changes, most of them being regressive, especially in the white matter, but numerous elements, detectable even with the common stains, showed hypertrophy of the cytoplasm and a

fairly well defined nucleus. These hypertrophic elements had a tendency to surround the blood vessels, but not in sufficient numbers to impress one as a definite perivascular accumulation.

The myelin sheaths were also slightly involved, especially around the blood vessels, where a gradual fading of the sheaths was detectable. This was not a massive disintegration of the myelin, but merely a rarefaction that was clearly demonstrable. The axis cylinders showed acute swelling, but only occasional disintegration.

Fat deposits were found surrounding the blood vessels and in the perivascular spaces in both the cortex and the white substance.

CASE 2.—*History.*—A. P., a white boy, 3 months of age, who was admitted to the hospital on May 8, 1930, at 12.15 a. m., had had no previous illness. Seven days

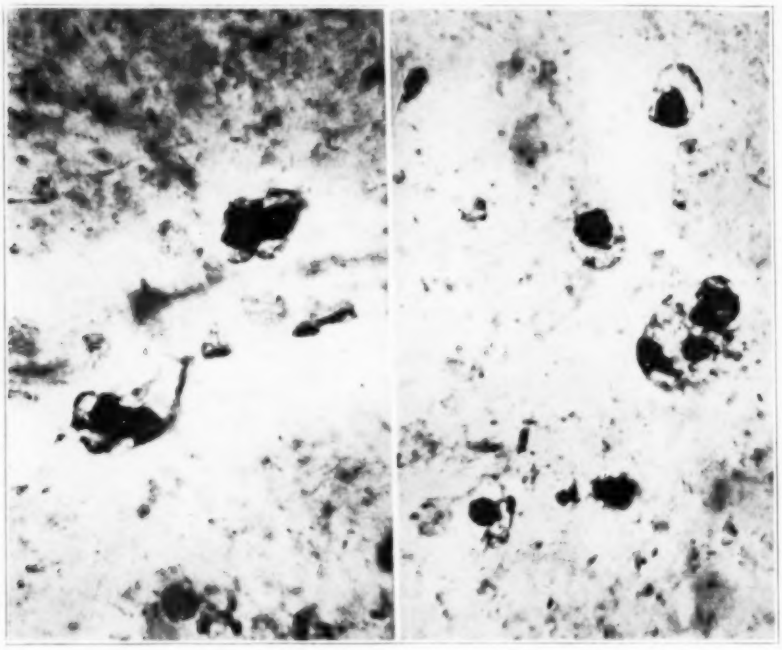


Fig. 5.—Oligodendroglia cells in a stage of acute swelling; del Rio Hortega silver carbonate method.

prior to admission, symptoms and a rash appeared which were diagnosed by the family physician as measles. On the night prior to admission, high fever developed, and a convulsion occurred.

Physical Examination.—The child was acutely sick and markedly dyspneic. There was a fading macular rash on the face, trunk and extremities. The pupils were equal and reacted to light and in accommodation; there was no nystagmus or strabismus; conjunctivitis was present. There was a slight nasal discharge. The tongue was coated. No Koplik spots were present on the buccal mucosa. The pharynx was congested, and there was a profuse nasal discharge. There was no adenopathy of note. There was no impairment of the percussion note over the lungs; the breath sounds were clear. The heart sounds were clear; the rate was rapid; no murmurs were heard. The abdomen was slightly distended and soft; no

masses were palpable; an umbilical hernia was present. A neurologic examination gave negative results. The temperature was 104.2 F.; the pulse rate was 162 and the respiration rate 62 per minute.

Lumbar puncture revealed a clear, watery cerebrospinal fluid under increased pressure; there were 8 cells per cubic millimeter; the sugar reaction was +++ (normal); the Pandy test was negative.

Course.—On May 8, 1930, at 9 a. m., the temperature was 104 F., the pulse rate 160 and the respirations 88 per minute. There was evidence of marked respiratory distress; the respirations were shallow, with an expiratory grunt and flaring of the alae nasi. The fontanel was soft and there was no bulging. There was no rigidity of the neck, and the Kernig sign was negative. There was impairment to percussion over the left side of the chest posteriorly; fine and coarse râles were heard over this area, and the breath sounds were moderately high-pitched. Coarse râles on

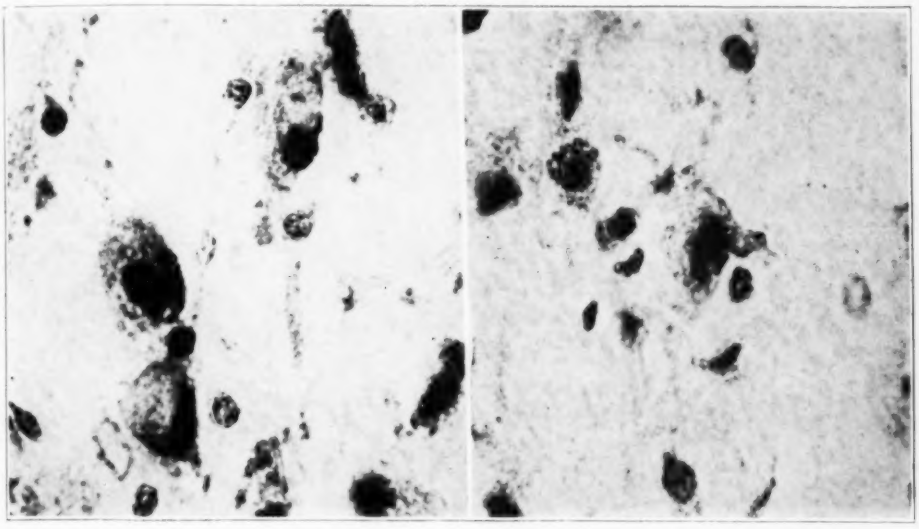


Fig. 6.—High power magnification showing details of the severe type of lesion of nerve cells; Nissl stain.

expiration were heard in the right axilla. The right ear drum was red and congested and the landmarks were obliterated, but there was no definite bulging; the left ear drum appeared to be normal.

On May 9, 1930, at 4 a. m., the patient was having convulsions at frequent intervals. The pulse was rapid and thready. The child was unable to swallow, mucus collecting in the pharynx. Death occurred at 5:45 a. m.

Clinical Diagnosis.—The clinical diagnosis was measles, bronchopneumonia and acute right otitis media.

General Autopsy (May 10, 1930; Dr. J. Werne).—The more significant observations were as follows: The anterior fontanel was normally patent. The dural sinuses were not remarkable. The surface blood vessels of the brain showed injection, and there was an excess of cerebrospinal fluid under tension. Serial sections through the brain substance revealed injection of the vascular markings with possibly focal hemorrhages.

Anatomic Diagnosis.—The anatomic diagnosis was: measles; bronchopneumonia; acute fatty infiltration of the liver; acute hyperplastic splenitis; early encephalitis.

Histologic Study of the Nervous System.—The lesions, present over all the cortex and the subcortical structures, were the expression of a very acute diffuse

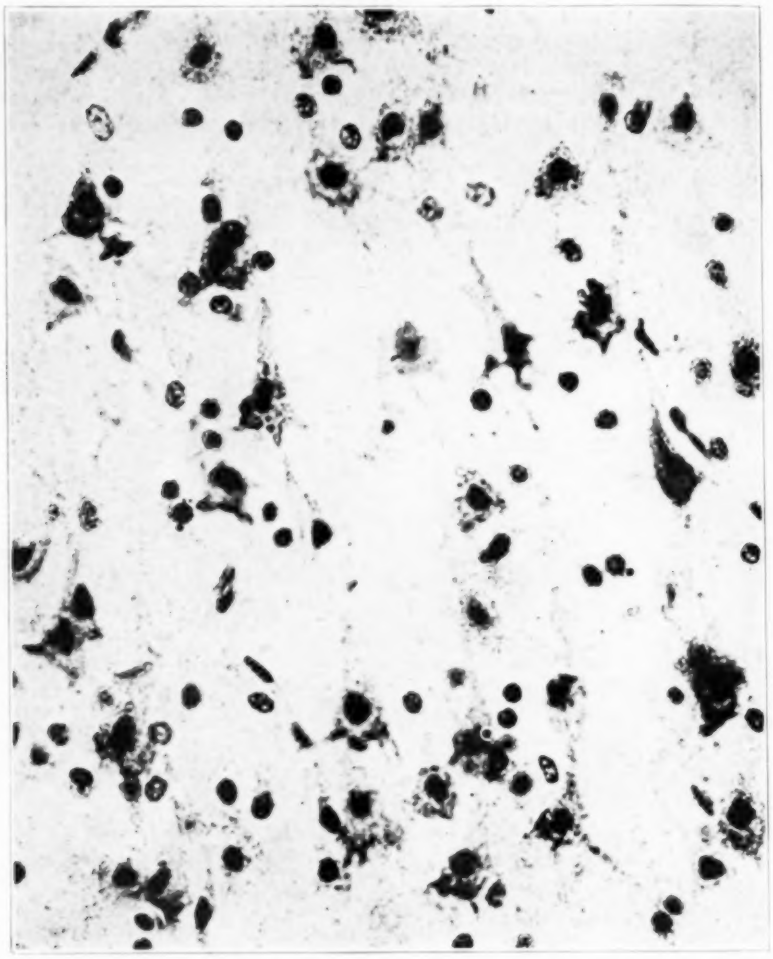


Fig. 7.—Diffuse ischemic changes of nerve cells in toxic encephalopathy, and transitional stage with a severe type of degeneration of cells; Nissl stain.

condition. With the Nissl stain, it was seen that the changes involved mainly the nerve cells and consisted in the severe type of degeneration of the nerve element described by Nissl; all gradations could be seen from acute swelling to complete disintegration. The nerve cell appeared more or less swollen, the processes were more evident, and the Nissl bodies had entirely disappeared, leaving a cytoplasm somewhat granular and showing here and there minute annular bodies. The nucleus did not constantly behave in the same way; at times, it was swollen, and

the nucleolus, very small, was still visible; at other times, the nuclear membrane underwent a process of shrinkage, while the nucleolus appeared enlarged; the whole nucleus, considerably reduced in size, was deeply stained and often was represented mainly by the enlarged nucleolus. Acellular areas were formed as the result of the disappearance of groups of disintegrated cells. With a high power, the nerve cells disclosed more visibly their disintegrated cytoplasm and the shrinkage of the

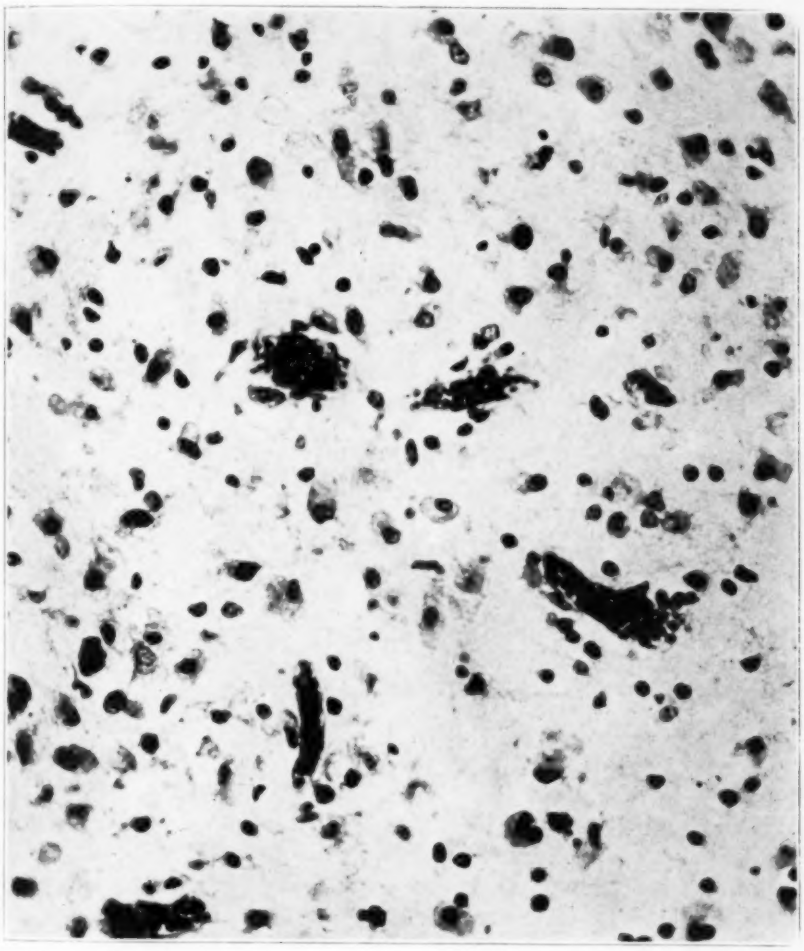


Fig. 8.—Progressive and regressive changes of neuroglia in the white substance. The cells involved are mainly located in the vicinity of and surrounding blood vessels.

nucleus (fig. 6). To undergo total disintegration the nerve cell did not have to pass necessarily through a stage in which the nucleus was shrunken and deeply stained, as shadows of cells were seen in which the nucleus was traceable as a large, clear pale-stained structure. Here and there cells were also found in a stage recalling the ischemic type of lesion described by Spielmeyer (fig. 7). These cells presented a

shrunken appearance with a deeply stained nucleus and disappearance of Nissl bodies. The cytoplasm was more uniform than in the severe type of degeneration and the cell body more uniformly triangular. It must be said, however, that the differentiation between the ischemic type and the severe type of degeneration of the nerve cell was at times difficult, as all transitional stages could be found between the two types of lesions.

The glial elements in the cortex disclosed pathologic changes, and with both Nissl and Cajal stains some astrocytes were seen undergoing combined progressive and regressive changes. The elements appeared hypertrophic, and their cytoplasm was voluminous in the central portion, while the periphery seemed to undergo a process of liquefaction.

With the specific stain for oligodendroglia, numerous swollen oligodendroglia cells were seen surrounding the nerve cells or blood vessels.

In the white substance there was also a considerable hypertrophy of astrocytes, detectable even with the Nissl method, consisting of an enlarged cytoplasm with a well defined nucleus filled with chromatin substance. Astrocytes with the progressive changes mentioned were numerous, but they tended to collect around some of the perivascular areas (fig. 8). Among the hypertrophic elements were many undergoing degenerative changes; a few cells were also transforming into reticular elements.

The blood vessels of both cortex and white substance were engorged with red cells, especially the veins, pointing to a venous stasis. Most of the blood vessels, especially in the outer layer of the cortex, had a swollen endothelium.

The myelin sheaths were slightly involved by the pathologic process, and with the Spielmeyer method in frozen sections, patches were detected in which staining was light; these corresponded to a process of rarefaction. There seemed to be a predilection of the lighter areas for the perivascular regions.

The axis cylinders presented an acute swelling, but no considerable disintegration.

With fat stains, no fat was encountered, generally speaking, in the reticular cells that have been described as present in the white substance, but in the cortex, as well as in the white substance, fat was present here and there in the perivascular sheaths. With the Fettponceau stain, little fat was demonstrated in comparison with the severity of the pathologic process.

COMMENT

The two cases described differed from those of the usual type of so-called encephalitis occurring in the course of measles in the following points: (1) the absence of perivascular proliferation of microglial elements, which is characteristic for measles encephalitis; (2) the absence of definite perivascular demyelinization and of perivascular disintegration of the axis cylinders; (3) the presence of a pronounced involvement of the gray matter, contrasting with the more pronounced involvement of the white substance in measles encephalitis.

On the other hand, there was a total absence of inflammatory lesions either in the meninges or in the brain parenchyma. The absence of any inflammatory reaction justifies, then, our use of the word encephalopathy instead of encephalitis.

The two cases seem to us to be of extreme importance because they prove that, in the course of measles, changes may occur in the brain that are entirely different from those usually described by the majority of authors. We are dealing here with a diffuse process of acute swelling and a severe type of lesion of the nerve cells which is detectable all over the cortex and the central structures. The type of lesion is comparable and even identical with the lesions that can be produced

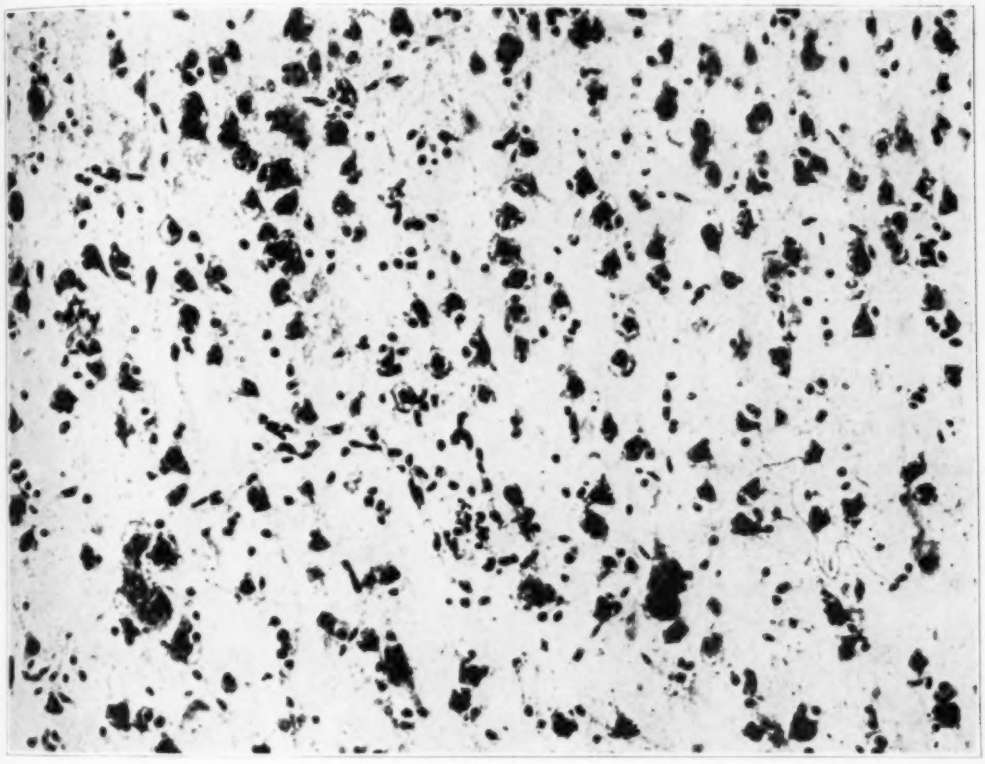


Fig. 9.—Diffuse liquefaction of nerve cells in experimental lead poisoning (cat); Nissl method for nerve cells.

experimentally by the use of an exogenous chemical agent; we refer to the lesions that are encountered in experimental lead poisoning. A comparison of the lesions in our cases with those observed in experimental lead poisoning, illustrated in figure 9, will demonstrate the difficulty of making a differential diagnosis between the two. This identity of the lesions seems to support the view that measles encephalitis is not an infectious condition but a toxic one. We have no doubt as to the soundness of this conclusion.

In the literature, we have found that von Economo [2] described cases, clinically diagnosed as encephalitis epidemica, in which histologic study revealed the absence of the typical inflammatory picture of epidemic encephalitis and the presence of diffuse edema of the brain substance associated with diffuse generalized cloudy swelling of the nerve cells and increase of the glial nuclei. According to von Economo, this picture occurs in the so-called hyperacute cases and is the expression of a more

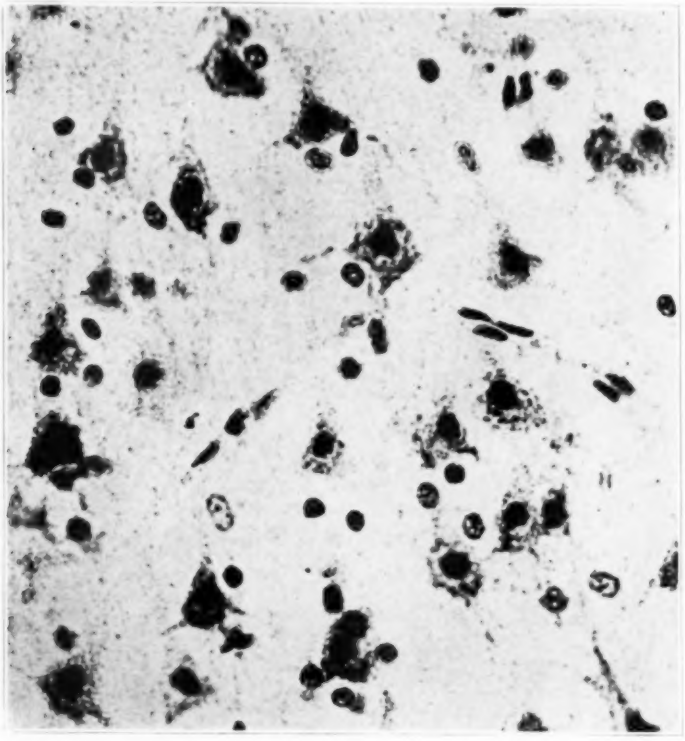


Fig. 10.—Severe type of lesion of nerve cells found in a case of encephalomyelitis in measles; Nissl method.

severe pathologic process, leading to death before the inflammatory reaction of the blood vessels develops.

We think that in our cases, also, the pathologic process was exceptionally severe, a hyperacute one, producing death in both cases approximately within thirty-six hours after the appearance of clinical manifestations pointing to an involvement of the central nervous system. The severity of the process, a toxic one, did not allow time for the

2. von Economo: Die Encephalitis Lethargica, Berlin, Urban & Schwarzenberg, 1929.

defense mechanism to enter into efficient action. This explains, on the one hand, the diffusion and the severity of the cortical involvement, which is not found in the less acute type of encephalitis, and, on the other hand, the absence of the characteristic perivascular proliferation of microglial elements. Had the process lasted a few more days and had it been less severe, we presumably would have had a typical picture of so-called measles encephalitis; this was manifested to some extent in our two cases by the tendency of the glial reaction to be more severe around the blood vessels and by the tendency toward demyelinization of the nerve fibers in the same areas.

The objection can be raised that in our two cases we are dealing with exceptional toxic causes, whereas in the common type of encephalitis there is an infectious condition. Against this dual conception is the fact that in some cortical areas in typical cases of measles encephalitis we have encountered the same fundamental type of severe lesion of the nerve cells as in the two cases here described (fig. 10) not complicated by other pathologic changes. On the other hand, the typical picture of measles encephalitis is certainly not of the usual inflammatory type that is seen in other infectious conditions. This fact alone should open the mind to the difference between the pathogenesis of measles encephalitis and that of other types of infectious encephalitis.

CONCLUSIONS

We therefore think that a toxic factor is the basis of the cerebrospinal manifestations occurring in the course of measles, and that if this factor is extremely powerful, all the elements, neuroglia and nerve cells undergo changes dominantly of the degenerative type, while if the intensity of this factor is moderate, the action will be fought in the perivascular areas, thus stimulating the defensive power of microglia cells, which therefore proliferate around the blood vessels.

THE ACTION OF CERTAIN DRUGS

ON THE CEREBROSPINAL FLUID AND ON THE INTERNAL JUGULAR VENOUS AND SYSTEMIC ARTERIAL PRESSURES OF MAN

JULIUS LOMAN, M.D.
AND
ABRAHAM MYERSON, M.D.
BOSTON

In a previous paper [1] we described the technic of measuring the pressure within the internal jugular vein and demonstrated that when combined with the cerebrospinal fluid and intracarotid pressures it constituted a clinical approach to the study of certain phases of the dynamics of the cerebral circulation.

Although the internal jugular vein lies outside the cranial cavity and does not measure accurately the true cerebral venous pressure, it lies so close to the cerebral sinuses that for all practical purposes we believe that the reading obtained at the site punctured (a matter of a few millimeters from the sinuses) must reflect closely the dynamics of the cerebral veins. Our previous experiments, recorded in the article cited, confirm this belief almost to the point of certainty, since those procedures, which in animals alter the pressure within the cerebral sinuses, alter the pressure within the human internal jugular vein in identical manner. Thus, we found that changing the position of the head altered the jugular venous pressure exactly as the cerebral venous pressure is altered in animals by a change of posture: to wit: lowering the head markedly increased the jugular venous pressure; raising the head diminished it. All violent expiratory efforts increased the jugular venous pressure exactly as these procedures altered it in the sinuses in animals. Ether raised the jugular venous pressure as the same drug raised the sinus pressure in experimental animals. Pressure on the abdomen, excitement, struggle and other pressures, which in animals elevated the sinus pressure, also elevated the venous pressure obtained in

---

Submitted for publication, Nov. 1, 1930.

From the Research Laboratory of the Boston State Hospital and the Department of Neurology, Tufts Medical School.

1. Myerson, A., and Loman, J.: Internal Jugular Venous Pressure in Man: Its Relation to Cerebrospinal Fluid and Carotid Arterial Pressures, Arch. Neurol. & Psychiat. **27**:836 (April) 1932.

the intracranial jugular vein, so that we concluded that the measurement of the pressure of the internal jugular vein is in fundamentals a measurement of the sinus pressure.

In any study of the dynamics of the brain it is essential, since the brain is peculiar in its physics, to measure the cerebral venous pressure rather than to depend on the general venous pressure; first, because the cerebrospinal fluid pressure has been found to be greatly dependent on that of the cerebral veins, and second, because the changes of pressure in the cerebral veins do not always run parallel to the changes in the general venous system. These facts have been amply demonstrated by Becht,[2] Weed [3] and others.

The purpose of this article is to report the effects of certain drugs on the cerebrospinal fluid, internal jugular venous and arterial pressures in man. All previous work of this nature has been done on animals under conditions that complicate the evaluation of the effects of the drugs. For example, ether has been the usual anesthetic administered to the animals. We have shown in a previous paper [1] that this drug in itself causes a marked increase of cerebrospinal fluid and internal jugular pressures; Forbes, Wolff and Cobb [4] have recently demonstrated that among the effects of this drug there is a marked vasodilatation of the cerebral vessels. These authors have shown further that there is a marked difference in the effect of histamine on the cerebral vessels and cerebrospinal fluid, depending on whether ether or amytal has been the anesthetic. We used no general anesthesia, and the only anesthetic utilized was procaine hydrochloride to desensitize the skin preparatory to the puncture of the internal jugular vein and the lumbar subarachnoid space.

The technic of obtaining the pressure in the internal jugular vein has been previously described.[5] The lumbar puncture is performed immediately before the jugular puncture and in the usual manner. Although it would be ideal to register the intracarotid pressure in preference to the general arterial pressure, we thought that this added puncture made the experiments too formidable as a routine procedure.

2. Becht, F. C.: Studies on the Cerebrospinal Fluid, Am. J. Physiol. **51**:1, 1920.

3. Weed, L. H.: Experimental Studies of Intracranial Pressure: Intracranial Pressure in Health and Disease, Baltimore, Williams & Wilkins Company, 1929, p. 25.

4. Forbes, H. S.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: X. The Action of Histamine, Am. J. Physiol. **89**:266, 1929. (This paper is one of a series of ten papers published by a research group working under the leadership of Dr. Stanley Cobb.)

5. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from the Internal Jugular Vein and Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807 (June) 1927.

All arterial pressure readings, therefore, were registered in the usual clinical manner with the sphygmomanometer. The subjects chosen were patients having some type of psychosis. None had any definite cardiovascular disease.

The only experiments here recorded are those in which the following conditions were fulfilled: (1) the patient was quiet and cooperative; (2) the needle entered the vein on the first attempt; (3) the blood oscillated in the manometer during the entire experiment; (4) at the completion of the observations, when the needle had been removed from the vein, the blood flowed freely through it and the manometer.

Under these conditions the experiments can be kept going for from five to ten minutes and occasionally longer. Because of the final clotting of the venous blood in the needle, it is often impossible to follow the complete cycle of pressure changes after the administration of the drug.

The cerebrospinal fluid, arterial and venous pressures were taken simultaneously at from one-half to one minute intervals. Before the administration of the drug, enough time was allowed for the cerebrospinal fluid and venous pressures to become adjusted and remain at constant levels.

EXPERIMENTS WITH EPINEPHRINE (TABLE 1)

Twelve experiments with epinephrine chloride (1:1,000) were performed. To obtain a rapid effect with this drug, from 0.3 to 0.5 cc. was injected intravenously. Within from ten to fifteen seconds (chart 1) there was a rapid rise in the cerebrospinal fluid, jugular and arterial pressures, all reaching their maximum pressures synchronously in from one to two minutes and gradually falling together. The cerebrospinal fluid pressure reached its original level within from five to ten minutes, in four cases returning to slightly below that level. The jugular reading fell to its initial pressure at about the same time. The arterial pressure, after increasing by from 50 to 124 mm. of mercury, gradually fell with the other two pressures and finally assumed a much lower level than its original one, showing the marked secondary depressor effect of epinephrine.

Such changes following the intravenous injection of epinephrine agree with those of most workers who utilized the torcular Herophili for their cerebral venous pressures.

That the rise in cerebrospinal fluid pressure results from the increased arterial pressure was definitely proved by an ingenious experiment by Becht.[2] Keeping the venous pressure at a constant level by allowing the torcular blood to overflow in a manometer, he showed that the cerebrospinal fluid pressure followed the rise in arterial pressure.

He concluded from his work that although the cerebrospinal fluid pressure usually depended on the cerebral venous pressure, it could also be directly affected by a sudden and great rise of arterial pressure.

Weed [3] also concluded from other experiments on animals that sudden changes in arterial pressure can directly affect the cerebrospinal fluid pressure.

A factor of importance in the dynamics of the cerebral circulation is the change in tonus of the cerebral vessels, which, by effecting changes in volume of the brain, tends to increase the intracranial pressure. Such changes are, of course, important in interpreting the cause of the rise in cerebrospinal fluid pressure. Vasodilatation of the cerebral vessels or a rise in the cerebral venous pressure will often account for such increases in cerebrospinal fluid pressure.

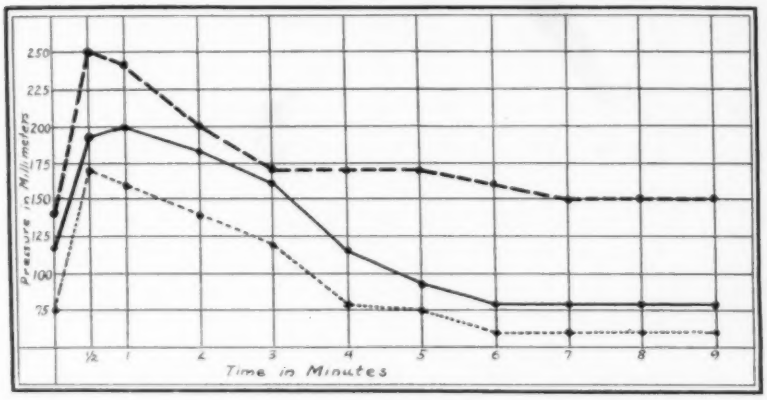


Chart 1.—Curves in a typical case, showing the effect of epinephrine hydrochloride, 0.3 cc. intravenously, on the pressures of the cerebrospinal fluid, the internal jugular vein and the brachial artery. In this and the succeeding charts, the broken line indicates the cerebrospinal fluid pressure in millimeters of cerebrospinal fluid; the dotted line, the internal jugular venous pressure in millimeters of blood, and the continuous line, the brachial arterial pressure in millimeters of mercury.

However, epinephrine causes vasoconstriction of the cerebral vessels and not vasodilatation, a fact we owe to the observations of Hirschfelder [6] and recently of Forbes and Wolff,[7] the latter using photographic and micrometric observations of the pial vessels. This vasoconstriction

6. Hirschfelder, A. D.: Effect of Drugs on the Vessels of the Pia Mater and Retina, J. Pharmacol. & Exper. Therap. **6**:597, 1915.

7. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

would in itself tend to lower the intracranial pressure, and thus lower the cerebrospinal fluid pressure.

We conclude, then, that the rise in cerebrospinal fluid pressure following the injection of epinephrine is a mechanical result of the great

TABLE 1.—*Effect of Epinephrine (0.3-0.5 Cc.) Intravenously on the Cerebrospinal Fluid, Internal Jugular Venous and Systemic Arterial Pressures*

Patient	Pressures*	Initial Pressure	½ Min.	1 Min.	2 Min.	3 Min.	4 Min.	5 Min.	6 Min.	7 Min.	8 Min.	9 Min.
R. C.	C.S.F.	140	250	240	200	172	172	172	160	150	150	150
0.3 cc.	I.J.V.	75	172	160	138	122	77	75	30	30	30	30
(chart 1)	S.A.	120	190	200	180	163	118	90	78	78	78	78
J. McG.	C.S.F.	240	...	350	350	270	270	240	240	230	235	235
0.3 cc.	I.J.V.	130	...	180	170	140	110	115	120	90	90	90
	S.A.	122	...	230	200	180	160	140	140	110	100	100
W. B.	C.S.F.	145	160	240	270	240	230	220	210	200	205	175
0.5 cc.	I.J.V.	40	80	140	160	160	150	140	120	110	100	100
	S.A.	108	110	102	190	182	160	120	98	76	76	68
H. H.	C.S.F.	180	...	310	300	260	240	220	210	200		
0.4 cc.	I.J.V.	80	...	100	110	115	115	100	90	80		
	S.A.	110	...	208	220	234	166	108	106	102		
H. B.	C.S.F.	165	...	200	200	185	175	150	130	130	135	130
0.3 cc.	I.J.V.	90	...	130	150	160	140	110	100	90	90	75
	S.A.	138	...	200	196	162	134	134	118	114	110	100
R. B.	C.S.F.	140	...	200	200	180	170	170	175	180		
0.3 cc.	I.J.V.	40	...	70	75	75	70	70	70	70		
	S.A.	108	...	158	140	140	100	78	80	84		
E. B.	C.S.F.	90	...	130	135	100	80	80	80	80		
0.3 cc.	I.J.V.	85	...	130	100	95	90	90	90	90		
	S.A.	110	...	170	202	140	98	96	90	90		
S. S.	C.S.F.	185	260	290	210	200	185	170	185			
0.4 cc.	I.J.V.	105	220	260	220	140	125	110	100			
	S.A.	128	150	172	155	143	135	130	125			
E. T.	C.S.F.	100	170	210	180	150	120	120	120			
0.3 cc.	I.J.V.	40	90	160	140	115	85	70	40			
	S.A.	118	198	162	148	134	112	108	108			
J. M.	C.S.F.	145	...	220	230	230	210	210	180	170	110	
0.5 cc.	I.J.V.	80	...	100	130	135	125	120	110	100	95	
	S.A.	120	...	200	210	200	188	136	114	86	80	
J. H.	C.S.F.	80	210	210	200	150	130	120	120			
0.5 cc.	I.J.V.	40	90	110	130	100	85	70	40			
	S.A.	118	180	184	174	150	134	104	80			
W. G.	C.S.F.	180	...	310	220	200	170					
0.5 cc.	I.J.V.	105	...	160	140	130	100					
	S.A.	132	...	174	170	122	118					

* In this and the succeeding tables, C.S.F. indicates cerebrospinal fluid; I.J.V., internal jugular venous, and S.A., systemic arterial.

and rapid rise in arterial pressure. The cerebral venous pressure also follows the arterial pressure.

EXPERIMENTS WITH AMYL NITRITE (TABLE 2)

We have seen that following the injection of epinephrine the cerebrospinal fluid pressure follows the arterial pressure. That this is seldom the case has been demonstrated by many investigators. The strongest evidence that there is little direct relationship between these

two pressures has come from the work of Becht.[2] In thirty-nine experiments that he performed, the arterial and cerebrospinal fluid pressures moved in the same direction thirty-eight times. Venous pressures also moved in the same direction. In fifteen other experiments, intracranial pressure followed venous pressure and not arterial pressure.

Thus, following the injection of amyl nitrite it is well established that although there is a drop in arterial pressure the cerebrospinal fluid pressure rises. The explanations of this rise in intracranial pressure, however, have not been in agreement.

Dixon and Halliburton,[8] using amyl nitrite, found, for example, a rise in cerebrospinal fluid pressure which came on immediately after

TABLE 2.—*Effect of Amyl Nitrite (0.3 Cc. by Inhalation) on the Cerebrospinal Fluid, Internal Jugular Venous and Systemic Arterial Pressures*

Patient	Pressures	Initial Pressure	½ Min.	1 Min.	2 Min.	3 Min.	4 Min.	5 Min.	6 Min.	7 Min.	8 Min.	9 Min.
S. S. (chart 2)	C.S.F.	85	130	240	200	175	165	135	120	110	110	110
	I.J.V.	70	100	140	130	110	100	90	85	85	90	90
	S.A.	116	100	76	78	78	80	80	85	85	80	94
W. L.	C.S.F.	170	350	350	330	270	260	210	210	160		
	I.J.V.	75	110	110	105	95	90	85	85	80		
	S.A.	114	108	110	124	130	130	130	124	114		
W. D.	C.S.F.	65	170	220	180	150	130	120	80			
	I.J.V.	60	110	120	115	110	105	95	90			
	S.A.	110	100	90	85	87	97	98	97			
R. B.	C.S.F	100	120	220	220	230	230	230	230	225	220	210
	I.J.V.	95	150	200	200	200	190	190	185	180	180	180
	S.A.	117	110	100	92	98	100	110	106	100	102	100
L. K.	C.S.F.	265	...	400	550	530	515	460	400	350	280	260
	I.J.V.	120	...	190	210	200	200	200	200	195	195	190
	S.A.	151	...	125	132	138	141	143	128	132	132	122
E. B.	C.S.F.	155	260	300	310	280	240	220	160			
	I.J.V.	80	100	130	130	120	100	90	85			
	S.A.	127	110	92	100	104	100	108	113			

the arterial pressure began to fall; also that these changes were often associated with a general rise in venous pressure. These authors, however, stated that the rise in cerebrospinal fluid pressure was greater than and out of all proportion to the rise in venous pressure. This was interpreted by them to mean that the drug stimulated cerebrospinal fluid formation.

Becht,[2] on the other hand, found that with amyl nitrite the cerebrospinal fluid pressure ran parallel with the venous pressure, and he concluded that all the changes in the behavior of the cerebrospinal fluid could be logically explained by changes in the arterial and venous pressures. He found, however, not a rise but a fall in cerebrospinal fluid pressure.

8. Dixon, W. E., and Halliburton, W. D.: The Cerebrospinal Fluid: II. Cerebrospinal Fluid Pressure, J. Physiol. **48**:129, 1914.

What these and other observers did not take into sufficient account was the effect of amyl nitrite on the caliber of the cerebral vessels with the inevitable volume change in the brain. That amyl nitrite causes vasodilatation of the vessels of the brain has been observed by many investigators. Including the older workers, Schuller [9] directly observed the brain through the intact dura and noted the universal dilatation of the cerebral vessels after the injection of amyl nitrite. Mosso [10] saw an increase in the bulk of the brain following the injection of amyl nitrite, and he concluded that the drug must cause a dilatation of the cerebral vessels. Shepard [11] came to a similar conclusion. Hirschfelder [6] observed the simultaneous dilatation of the vessels of both the retina and the cerebrum. Raphael and Stanton,[12] Florey,[13] Leake and others [14] also noted similar changes in the brain following the use of amyl nitrite.

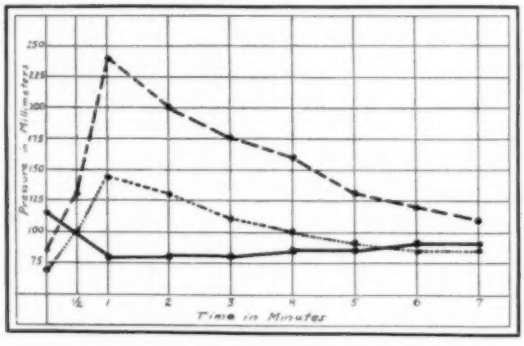


Chart 2.—Curves in a typical case, showing the effect of amyl nitrite, 0.3 cc. by inhalation, on the pressures of the cerebrospinal fluid, the internal jugular vein and the brachial artery.

Wolff,[15] by actual measurement of the changes in caliber of the pial vessels, observed that they dilated simultaneously with a fall in the systemic arterial pressure and a rise in cerebrospinal fluid pressure.

9. Schuller, M.: Berl. klin. Wchnschr. **11**:294, 1874.

10. Mosso: Ueber den Kreislauf des Blutes im menschlichen Gehirn, Leipzig, 1881.

11. Shepard, J. E.: The Circulation and Sleep: Experimental Investigations, New York, The Macmillan Company, 1914.

12. Raphael, T., and Stanton, J. M.: The Action of Certain Drugs on Brain Circulation in Man, Arch. Neurol. & Psychiat. **2**:389 (Oct.) 1919.

13. Florey, H. W.: Brain **48**:43, 1925.

14. Leake, C. D.; Loevenhart, C. S., and Muehlberger, C. W.: Dilatation of Cerebral Blood Vessels as a Factor in Headache, J. A. M. A. **88**:1076 (April 2) 1927.

15. Wolff, H. G.: The Cerebral Circulation: XI c. The Action of Amyl Nitrite, Arch. Neurol. & Psychiat. **22**:695 (Oct.) 1929.

We performed six perfect experiments with amyl nitrite. Within half a minute following the inhalation of 0.3 cc. of this drug there was a rapid rise in the cerebrospinal fluid pressure, which reached its maximum within about one minute from the beginning of the inhalation. By the time this had occurred, the jugular pressure had reached its maximum, and the arterial pressure had dropped to its minimum reading. All the patients reacted in a similar manner to the administration of the drug.

The cerebrospinal fluid and jugular curves showed a direct relationship in their rise and fall, gradually returning to their original levels in from five to twelve minutes, the cerebrospinal fluid finally occupying a slightly higher level than at the beginning of the experiment. The general arterial pressure after falling returned gradually, but remained lower than its original level at a time when the other two pressures had come close to their first readings.

To sum up: Following the inhalation of amyl nitrite, there is a rise in intracranial pressure and internal jugular venous pressure with a coincident fall in general arterial pressure. According to the work of Wolff [15] and others, simultaneous with these changes there is a vasodilatation of the cerebral vessels. This dilatation acts to increase the bulk of the brain, thus forcing the cerebrospinal fluid out of the subarachnoid spaces.

Amyl nitrite thus affords a classic example of the direct relationship between the cerebral venous (jugular) and the cerebrospinal fluid pressure and the divorce of the cerebrospinal fluid pressure from the arterial pressure.

EXPERIMENTS WITH SOLUTION OF PITUITARY (TABLE 3)

The extract of the pituitary gland has been utilized by several investigators in experiments on the cerebrospinal fluid. There has been general agreement that solution of pituitary causes a rise in intracranial pressure. The cause of this rise, however, has been variously interpreted. Weed and Cushing,[16] for example, believed that posterior lobe extract stimulates the secretory activity of the choroid plexus and concluded that the increase of fluid was independent of hemodynamic reactions. They did not, however, measure the cerebral venous pressure.

Dixon and Halliburton [17] agreed with these authors, but stated that if the animal is deeply anesthetized and artificially ventilated, pituitary extracts produce no increased outflow. They thought that the increased

16. Weed, L. H., and Cushing, Harvey: Studies on the Cerebrospinal Fluid: VIII. The Effect of Pituitary Extract upon Its Secretion (Choroidorrhoea), Am. J. Physiol. **36**:77, 1914-1915.

17. Dixon, W. E., and Halliburton, W. D.: J. Physiol. **50**:198, 1915; footnote 8.

outflow seen in the normally breathing animal is due to asphyxia because of bronchial constriction.

Becht and Matill [18] criticized these views and concluded from their work that the changes in the cerebrospinal fluid pressure could be all satisfactorily explained on a mechanical basis; that is, that the intracranial pressure followed the cerebral venous pressure.

As to the effect of the extract on the vessels of the brain, there is also some difference of opinion. Raphael and Stanton,[12] observing the changes in the volume of the brain through a defect in the skull in man, concluded that a solution of pituitary given intravenously caused cerebral vasodilatation.

Florey [13] noted no variation in the size of the cerebral vessels in cats either on local application of solution of pituitary or on intravenous injection. Sandor,[19] using direct microscopic observation, noted that

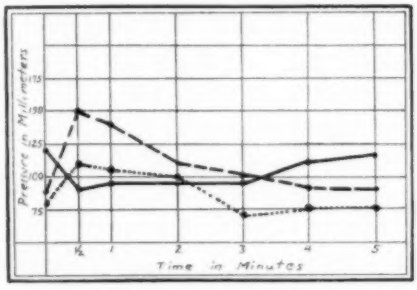


Chart 3.—Curves in a typical case, showing the effect of solution of pituitary, 1 cc. intramuscularly, on the pressures of the cerebrospinal fluid, the internal jugular vein and the brachial artery.

solution of pituitary caused constriction followed by dilatation of the cerebral vessels in the frog. No changes in the cerebral arteries in cats were seen by Howe and McKinley [20] after intravenous injections of pitutitary extracts.

More recently, Wolff,[21] using direct microscopy through a window screwed into a trephine hole in the skull, made local applications and intravenous injections of the posterior lobe of the pituitary gland. He concluded that the extract caused constriction of the pial vessels of all

18. Becht, F. C., and Matill, P. M.: Studies on the Cerebrospinal Fluid: VI. Study of Tissue Extracts, Am. J. Physiol. **51**:122, 1920.

19. Sandor, G.: Arch. f. d. ges. Physiol. **213**:492, 1926.

20. Howe, H. S., and McKinley, E.: Cerebral Circulation, Arch. Neurol. & Psychiat. **18**:81 (July) 1927.

21. Wolff, H. G.: The Cerebral Circulation: XI b. The Action of the Extract of the Posterior Lobe of the Pituitary Gland, Arch. Neurol. & Psychiat. **22**:691 (Oct.) 1929.

sizes. This vasoconstriction, however, was never striking, although definite. Wolff found that after intravenous injection of the drug there was a rise in arterial blood pressure and vasoconstriction of the blood vessels. These changes were accompanied by a brief fall in cerebrospinal fluid pressure during the maximal vasoconstriction and followed by a rise in intracranial pressure as long as the elevation of systemic blood pressure continued.

From these experiments, then, there appeared to be a direct relationship between the arterial and intracranial pressures. However, Wolff did not measure the cerebral venous pressure in these experiments.

TABLE 3.—*Effect of Solution of Pituitary (1 Cc. Intravenously) on the Cerebrospinal Fluid, Internal Jugular Venous and Systemic Arterial Pressures*

Patient	Pressures	Initial Pressure	½ Min.	1 Min.	2 Min.	3 Min.	4 Min.	5 Min.	6 Min.	7 Min.	8 Min.	9 Min.
H. B.	C.S.F.	120	...	230	200	180	160	150	140			
	I.J.V.	70	...	150	130	125	120	100	90			
	S.A.	130	...	128	126	132	130	130	128			
D. B.	C.S.F.	110	150	130	110	100	115	105	100			
	I.J.V.	75	90	80	75	70	75	75	75			
	S.A.	145	155	150	150	145	145	145	147			
J. M.	C.S.F.	85	170	150	130	110	110	100				
	I.J.V.	80	110	100	90	90	80	75				
	S.A.	128	88	90	85	85	84	84				
T. A.	C.S.F.	70	145	150	140	140	140	135	140	140	130	120
	I.J.V.	55	65	70	75	70	70	70	70	70	65	60
	S.A.	100	80	75	75	75	75	80	80	93	90	90
R. C.	C.S.F.	160	240	200	185	190	180	190	180	190		
	I.J.V.	90	150	140	125	130	130	120	125	125		
	S.A.	155	120	115	105	105	100	105	105	100		
H. B. (chart 3)	C.S.F.	90	150	135	110	102	90	90				
	I.J.V.	80	110	105	100	70	75	75				
	S.A.	120	90	95	95	95	110	112				
D. F.	C.S.F.	60	...	100	80	70	75	80				
	I.J.V.	40	...	85	80	75	75	75				
	S.A.	110	...	90	90	84	80	80				

Using the same brand of solution of pituitary as Wolff (pituitrin, obstetric, Parke, Davis and Company), seven patients were given intravenous injections of 1 cc. of this solution. In five of the seven patients there was a marked depressor effect on the arterial pressure in contrast to the usual pressor effect of this drug obtained by Wolff in his experiments. In one of the other two cases there was a slight pressor effect, and in the remaining instance practically no change in the arterial pressure occurred.

That pituitary extracts have variable effects on the vascular system has been noted by several observers. Jacobson,[22] testing the various extracts, concluded that there is a marked variability in the hemodynamic reaction on intravenous injection. In general, he found that the posterior lobe exhibits a moderate depressor effect followed by a spe-

22. Jacobson, C.: Haemodynamic Reactions of Hypophysial Extracts, Bull. Johns Hopkins Hosp. **31**:185 (June) 1920.

cific pressor effect. Roth [23] found that the character of the blood pressure tracing caused by several preparations of pituitary extract varied greatly.

Following the injection of the extract into our subjects, there was a rise, within thirty seconds, of cerebrospinal fluid and jugular venous pressures. Coincident with these changes, in the five cases there was a drop in arterial pressure to or near its lowest point during the experiment; nor was the fall in blood pressure a slight one. The drop in the five cases ran as follows: 55, 44, 26, 25 and 30 mm. of mercury, respectively.

The arterial pressure, after falling suddenly, gradually rose as the cerebrospinal fluid and venous pressures fell after their sudden rise. Owing to the fact that the effect of solution of pituitary usually lasts several minutes, observations of the complete cycle of changes could not be followed except in two cases. In these, the effects of the drug wore off in about five minutes.

The usual formula of the three pressure reactions in our experiments with solution of pituitary, then, was a rise of cerebrospinal fluid and jugular venous pressures with a fall of arterial pressure. It is seen that the rise in intracranial pressure is not related to the arterial pressure, for whether the latter rises (Wolff's experiments) or falls, there is usually a rise in the former pressure. In either case, i. e., whether the arterial pressure rises or falls, the internal jugular venous pressure is always parallel to the cerebrospinal fluid pressure. This agrees with Becht's assertion that there is a direct relationship between the cerebral venous and cerebrospinal fluid pressures.

As already noted, Wolff found that a slight vasoconstriction of the venous vessels was accompanied by a rise in arterial pressure. Under such conditions one does not expect an increase in volume of the brain; in fact, a slight decrease in volume occurs. Therefore, if there was vasoconstriction in our cases together with a fall in blood pressure, the rise in cerebrospinal fluid pressure must be explained on some, to us unknown, basis. It is likely that in these cases, with the fall in arterial pressure, there was not a vasoconstriction, but instead, a vasodilatation, with a resulting increase in brain volume with a rise in cerebrospinal fluid pressure.

That such were the physical changes in the brain is supported by the work of Hirschfelder,[6] who observed the vessels of the pia mater of the cat while at the same time recording the carotid pressure. He noted that vasoconstriction accompanied by a rise in general arterial pressure could be regarded as a proof of vasoconstriction of the pial

23. Roth, G. B.: The Several Factors Involved in the Standardization of Pituitary Extracts, J. Pharmacol. & Exper. Therap. **6**:595, 1915.

vessels, and likewise that a vasodilatation accompanied by a fall in general arterial pressure was invariably accompanied by general dilatation of the pial vessels.

Thus there may be two sets of reactions following the injection of solution of pituitary: (1) a vasoconstriction with a rise in arterial blood pressure with the resultant mechanical rise in venous and cerebrospinal fluid pressures, and (2) a vasodilatation plus a fall in arterial pressure, but with a resultant increase in the volume of the brain and a rise in internal jugular venous and cerebrospinal fluid pressures.

EXPERIMENTS WITH HISTAMINE (TABLE 4)

The only records of simultaneous cerebral venous, cerebrospinal fluid and arterial pressures under the effect of histamine were made by Lee.[24] He found that when this drug was injected into a vein of cats or dogs there was a fall in all three pressures. (This author utilized the sagittal sinus vein for the cerebral venous pressure.) He concluded from this that the cerebrospinal fluid pressure fell as a result of the fall in arterial pressure. There was one important fact that Lee did not take into consideration: His animals were given ether before the administration of the histamine. Under the influence of this anesthetic, the cerebral vessels become dilated, and when histamine is given the vessels constrict and the cerebrospinal fluid falls (Forbes, Wolff and Cobb[4]).

We have noted also that under ether[1] patients exhibit a simultaneous rise in internal jugular venous and cerebrospinal fluid pressures in spite of the fact that the arterial pressure falls at the same time. Forbes, Wolff and Cobb[4] observed that, when the animals were already under the effects of amytal, with the injection of histamine there was an increase in cerebrospinal fluid pressure coincident with great pial vasodilatation, a drop in systemic arterial pressure and a rise in systemic venous pressure. They did not record the cerebral venous pressure.

Other observers have noted the increase in cerebrospinal fluid pressure following the injection of histamine. Among them, Weiss, Lennox and Robb[25] found a rise in this pressure in sixty nonanesthetized patients who were given small doses of histamine intravenously.

What happens to the brain under the influence of this drug was observed by Weiss in a patient during an operation on the head. The patient was under phenobarbital and paraldehyde narcosis. Following a small intravenous dose of histamine, he observed a marked bulging

24. Lee, F. C.: Effect of Histamine on Cerebrospinal Fluid Pressure, Am. J. Physiol. **74**:317 (Oct.) 1925.

25. Weiss, S.; Lennox, H. G., and Robb, G. P.: Dilator Effect of Histamine on the Cerebral Vessels in Man, Proc. Soc. Exper. Biol. & Med. **26**:706, 1928-1929.

of the brain upward into the decompressed area, a marked flushing of the vessels and pulsation of the brain.

There is little doubt, then, that histamine causes a vasodilatation with a consequent increase in the brain volume.

Seven-tenths milligram of histamine (imido-Roche) was injected intramuscularly into nine patients in whom the conditions of the experiments were ideal. The following results were obtained: 1. In every instance there was a sharp rise in cerebrospinal fluid pressure which began in less than thirty seconds and reached its peak in from two

TABLE 4.—*Effect of Histamine (0.7 Mg. Intramuscularly) on the Cerebrospinal Fluid, Internal Jugular Venous and Systemic Arterial Pressures*

Patient	Pressures	Initial Pressure	½ Min.	1 Min.	2 Min.	3 Min.	4 Min.	5 Min.	6 Min.	7 Min.	8 Min.	9 Min.
S. G.	C.S.F.	160	185	350	280	260	260	220	210	200	190	
(chart 4)	I.J.V.	65	70	70	70	70	70	70	70	70	70	
	S.A.	100	88	80	82	82	88	88	88	88	88	
A. F.	C.S.F.	160	...	270	230	210	190	180	180	150	140	140
(chart 5)	I.J.V.	130	...	120	120	120	110	100	100	90	80	70
	S.A.	98	...	94	98	100	98	98	98	85	85	85
R. B.	C.S.F.	170	...	260	200	260	230	220	210	190	180	170
	I.J.V.	90	...	80	80	80	80	75	75	75	75	75
	S.A.	90	...	90	92	90	90	84	92	94	94	90
T. O'B.	C.S.F.	110	...	150	155	150	150	150	150	135	115	120
	I.J.V.	80	...	80	70	65	60	65	65	70	70	60
	S.A.	124	...	120	120	118	110	112	108	108	110	112
J. P.	C.S.F.	70	150	140	140	150	150	140	150	140	150	130
	I.J.V.	85	85	90	90	90	90	90	85	80	70	70
	S.A.	124	110	104	110	106	110	110	110	110	110	110
M. G.	C.S.F.	90	...	140	180	170	150	150	155	145	150	135
	I.J.V.	80	...	85	70	70	70	75	80	80	80	80
	S.A.	150	...	132	128	120	120	120	124	124	130	146
H. H.	C.S.F.	195	...	350	310	250	225	225	215	215	195	210
	I.J.V.	90	...	85	80	80	85	85	80	80	80	80
	S.A.	120	...	110	110	112	110	108	110	112	110	110
H. H.	C.S.F.	160	200	350	320	260	245	235	235	210		
	I.J.V.	80	80	80	80	80	80	80	80	80		
	S.A.	120	120	104	108	108	108	107	110	110		
H. B.	C.S.F.	80	...	100	110	100	100	90	80	75	75	50
	I.J.V.	70	...	70	70	70	70	70	75	75	75	75
	S.A.	136	...	126	118	112	112	116	120	120	120	120

to three minutes and then gradually fell, approaching its initial level in from ten to twenty minutes.

2. The arterial pressure fell in every case, but not remarkably. The greatest drop, in one case, was 30 mm. of mercury. In two cases there was a fall of only 4 and 6 mm. of mercury, respectively. The average drop was 15 mm.

3. The internal jugular venous pressure registered as follows: It remained practically unchanged or else it decreased while the cerebrospinal fluid was rising, so that by the time the latter pressure had returned to its original level the jugular pressure was the same or lower than its initial reading. In other words, the cerebrospinal fluid pressure followed neither in the direction of the arterial pressure nor in that of the jugular venous pressure.

Such a lack of relationship of the cerebrospinal fluid pressure to either the venous or the arterial pressure in these experiments is contrary to what one would expect. In comparing, for example, histamine

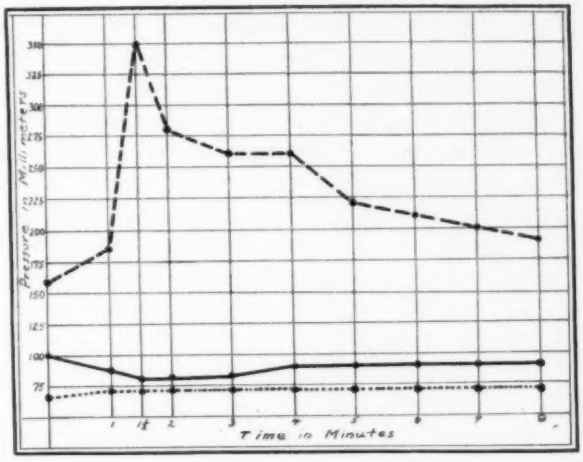


Chart 4.—Curves in a case, showing the effect of histamine, 0.7 mg. intramuscularly, on the pressures of the cerebrospinal fluid, the internal jugular vein and the brachial artery.

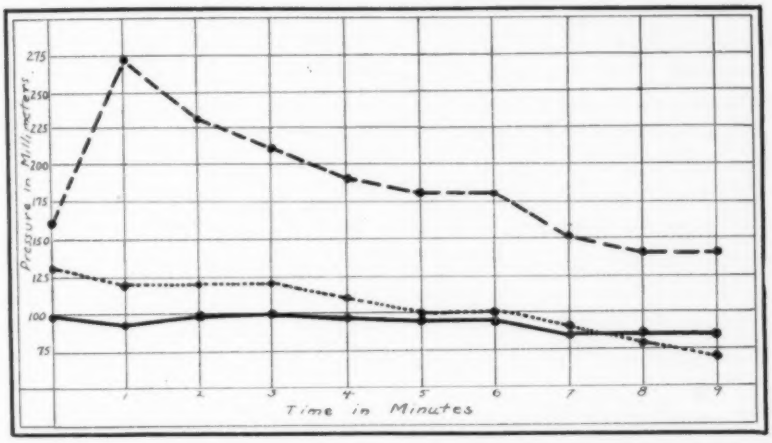


Chart 5.—Curves in a case, showing the effect of histamine, 0.7 mg. intramuscularly, on the pressures of the cerebrospinal fluid, the internal jugular vein and the brachial artery.

with amyl nitrite with respect to their arterial pressure and vasomotor changes, similar alterations in their respective cerebrospinal fluid and jugular venous pressure alterations might reasonably be anticipated.

Were it not for the fact that the cerebral vessels under histamine have been seen to dilate, we might be tempted to explain the rise of cerebrospinal fluid pressure with histamine on a secretory basis rather than on a mechanical, hemodynamic basis.

Thus, Dixon and Halliburton,[8] observing the effect of various drugs on the cerebrospinal fluid, torcular and arterial pressures, concluded that the rise in cerebrospinal fluid pressure was not a passive but rather an independent rise and should therefore be explained on a secretory basis. Again, Weed and Cushing,[16] using pituitary extract, believed that this drug caused a choroidorrhea and that the increase of cerebrospinal fluid was independent of blood pressure changes. These authors did not measure, however, the cerebral venous pressure, nor did they or Dixon and Halliburton have the advantage of observing the cerebral vessels under the action of the drugs they used.

Returning to the cause of the divorce in relationship between the cerebrospinal fluid and internal jugular venous pressures with the injection of histamine in man, there is one factor that has not yet been considered: the rate of flow of the blood. Is there a difference in the rate of blood flow, for example, following the injection of amyl nitrite and histamine, even though there is a vasodilatation with a drop in blood pressure in the case of both drugs? Without any data on this matter we cannot advance any explanation of the phenomenon of lack of relationship between the cerebrospinal fluid and vascular pressures. The only suggestion that we can make is that offered by the work of Bronk and Gesell.[26] These authors found that a more rapid flow through the head was accompanied by a less rapid flow through the extremities, and vice versa. Keeping this in mind, it may be that in the case of amyl nitrite the mechanism involved in the increased intracranial pressure works as follows: a vasodilatation with a resulting slowing up of the venous flow with congestion and a consequent rise in venous pressure; while in the case of histamine, the mechanism of increased pressure is the result of vasodilatation with an increased rate of flow of the venous blood, so that the venous pressure remains the same or is even diminished. How this hypothetic increased flow is brought about we cannot say.

A second factor that must be considered in this connection is the size of the dose of histamine. McDowell,[27] for example, found that in dogs and cats under light ether anesthesia, a small dose of histamine caused a rise in venous pressure. As the dose was increased, the rise became

26. Bronk, D. W., and Gesell, R.: Low Alveolar Oxygen Pressure: Sodium Cyanide and the Carotid and Femoral Flow of Blood, Proc. Soc. Exper. Biol. & Med. **24**:257, 1926.

27. McDowell, R. J. S.: Nature of Histamine Action, J. Physiol. **57**:146 (March) 1923.

less, and when the shock dose was approached, there was usually a fall in venous pressure.

These two factors, namely, the rate of blood flow through the brain and the size of the dose, may account for the difference in the reaction of the jugular venous pressure with histamine and such a drug as amyl nitrite. Accepting the internal jugular venous pressure as reflecting changes in the cerebral venous pressure, we may conclude that the reaction of histamine is one exception to the rule that the cerebrospinal fluid follows either the cerebral venous pressure or the general arterial pressure.

EXPERIMENTS WITH CAFFEINE (TABLE 5)

Thus far we have considered drugs that increase the pressure of the cerebrospinal fluid. As a drug having a known opposite effect we chose caffeine. That caffeine lowers the cerebrospinal fluid pressure has been definitely proved. Stephenson, Christensen and Wortes,[28] who made tracings of the cerebrospinal fluid pressure in two patients with cerebral

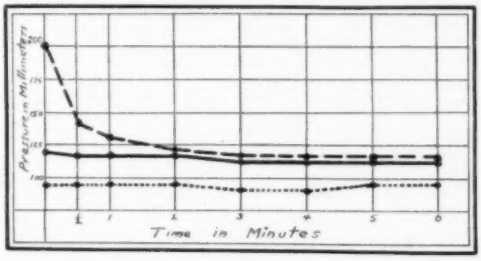


Chart 6.—Curves in a typical case, showing the effect of caffeine sodium benzoate, 0.5 Gm. intravenously, on the pressures of the cerebrospinal fluid, the internal jugular vein and the brachial artery.

hernias following decompression operations, noted a fall in this pressure after the injection of caffeine. Recently, Denker [29] studied the effect of the drug on fifty patients. In forty-nine of these subjects he noted a fall of cerebrospinal fluid pressure. Caffeine, because of this action, is now being used in some hospitals as a means of lowering increased intracranial pressure.

Nine perfect experiments were performed in our series of cases. In three cases, 0.5 Gm., and in the other six, 1 Gm., of caffeine sodium benzoate was injected intravenously. In every instance there was a drop in the intracranial pressure, in most cases the drop being gradual and beginning within one minute.

---

28. Stephenson, L.; Christensen, B., and Wortes, S. B.: Some Experiments in Intracranial Pressure in Man During Sleep, Am. J. M. Sc. **178**:663, 1929.

29. Denker, P. G.: The Effect of Caffein on the Cerebrospinal Fluid Pressure, Am. J. M. Sc. **181**:675 (May) 1931.

Although there was an average fall of 36 per cent in this pressure, the jugular venous reading remained practically unchanged during the entire experiment. The systemic arterial pressure registered no consistent changes, there being a fall in two cases, a rise in four and practically no variation in the three others.

Caffeine, then, is another drug that causes no corresponding alterations in cerebrospinal fluid and internal jugular or general arterial pressures.

TABLE 5.—*Effect of Caffeine (0.5 to 1 Gm. Intravenously) on the Cerebrospinal Fluid, Internal Jugular Venous and Systemic Arterial Pressures*

Patient	Pressures	Initial Pressure	½ Min.	1 Min.	2 Min.	3 Min.	4 Min.	5 Min.	6 Min.	7 Min.	8 Min.	9 Min.
M. D.	C.S.F.	110	...	120	100	75	70	65	75	65		
1 Gm.	I.J.V.	70	...	70	70	65	70	70	70	70		
	S.A.	128	...	148	120	110	108	108	108	108		
L. C.	C.S.F.	270	...	240	200	190	195	190	190	185	175	180
1 Gm.	I.J.V.	185	...	180	180	180	185	180	180	180	180	170
	S.A.	128	...	148	144	142	142	144	146	140	140	140
A. F.	C.S.F.	190	180	150	120	120	115	110				
1 Gm.	I.J.V.	90	90	90	90	95	90	90				
	S.A.	90	86	75	80	82	83	87				
M. G.	C.S.F.	150	155	140	130	115	120	120	125	130	135	150
0.5 Gm.	I.J.V.	90	90	90	90	90	90	90	90	90	90	90
	S.A.	110	118	108	108	110	118	120	120	118	118	110
H. B.	C.S.F.	140	...	110	90	90	80	80	90			
0.5 Gm.	I.J.V.	95	...	95	95	95	95	95	95			
	S.A.	122	...	134	130	134	134	134	136			
E. B.	C.S.F.	200	140	130	120	115	115	115	115	125	125	120
0.5 Gm.	I.J.V.	95	95	95	95	85	85	95	95	85	90	90
(chart 6)	S.A.	122	116	118	118	116	116	116	116	118	118	118
P. D'A.	C.S.F.	175	...	155	140	155	145	145	145	135	135	125
1 Gm.	I.J.V.	110	...	110	105	105	110	110	110	105	105	105
	S.A.	120	...	120	125	120	125	127	125	125	130	123
H. B.	C.S.F.	150	...	150	135	125	135	140	135	130	140	145
1 Gm.	I.J.V.	90	...	95	95	95	95	95	95	95	90	90
	S.A.	136	...	140	136	132	130	130	130	130	130	132
R. B.	C.S.F.	140	...	130	125	105	100	90				
1 Gm.	I.J.V.	90	...	90	90	90	90	90				
	S.A.	124	...	110	108	110	108	110				

Observations have been made by several workers concerning the effect of caffeine on the cerebral vessels. Hirschfelder,[6] directly observing the pial and retinal vessels, noted a vasodilatation after the injection of the drug. Sollmann and Pilcher [30] and Amsler and Pick [31] have also noted the same phenomenon. Were this the dominant action of caffeine, one would expect an increase rather than a decrease in the

30. Sollmann, T., and Pilcher, J. D.: The Action of Caffein on the Mammalian Circulation, J. Pharmacol. & Exper. Therap. **3**:19, 1911.

31. Amsler, C., and Pick, E. P.: Pharmakologische Studien am isolierten Splanchnikasgefassebiet des Frosches, Arch. f. exper. Path. u. Pharmakol. **85**:61, 1919.

cerebrospinal fluid pressure because of the generally observed increase of the cerebrospinal fluid pressure with an increase of brain volume.

That caffeine has a definite diuretic action has been demonstrated among other pharmacologists by Sollmann, Meyer and Gottlieb, and Cushny. Schroeder [32] noted that after caffeine diuresis the water content of rabbits' blood decreased by 10 per cent. Another important observation along this line was made by von Sobieranski.[33] He found that there was a great deal of difference in the diuresis, depending on whether rabbits were dry fed or wet fed; in other words, that in the absence of sufficient water in the tissues caffeine diuresis does not occur.

Thus, it is possible that if water is withdrawn from the blood by caffeine diuresis, there will be a corresponding withdrawal of fluid from the other tissues, including the brain.

Analogous changes apparently occur under the effect of hypertonic solutions. Weed and McKibben [34] made the historic observation that there is a marked diminution in brain bulk when intravenous injections of hypertonic solutions are given.

Later, Weed and Hughson,[35] taking simultaneous records of the cerebral-arterial, venous and cerebrospinal fluid pressures came to the conclusion that the alterations of the cerebrospinal fluid pressure were in large part independent of the alterations in the arterial and venous pressures of the brain. They found only a slight fall in the sagittal venous pressure, while the intracranial pressure fell markedly. Foley and Putnam [36] repeated the experiments of Weed and Hughson and came to a similar conclusion in regard to the lack of relationship between the three pressures.

The main effect of caffeine on the brain, then, appears to be the diminution of volume by its diuretic effect, this latter action overshadowing the effect of cerebral vasodilatation.

This mechanism, then, probably accounts for the fall in cerebrospinal fluid pressure.

---

32. Schroeder, W.: Ueber die Wirkung des Caffeins als Diureticum, Arch. f. exper. Path. u. Pharmakol. **24**:85, 1887.

33. von Sobieranski, W.: Ueber die Caffein Diurese, Arch. f. exper. Path. u. Pharmakol. **35**:144, 1895.

34. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injections of Solutions of Various Concentrations, Am. J. Physiol. **48**:512, 1919.

35. Weed, L. H., and Hughson, W.: Systemic Effects of the Intravenous Injections of Solutions of Various Concentrations with Especial Reference to the Cerebrospinal Fluid, Am. J. Physiol. **58**:53, 1921-1922.

36. Foley, F. E. B., and Putnam, T. J.: The Effect of Salt Ingestion on Cerebrospinal Fluid Pressure and Brain Volume, Am. J. Physiol. **53**:464, 1920.

CONCLUSIONS

1. Epinephrine causes a rise in intracranial pressure, together with a rise of arterial and internal jugular venous pressures. The rise in intracranial pressure is probably due to the sharp rise in arterial pressure, since there is a vasoconstriction of the cerebral blood vessels.

2. Amyl nitrite causes a rise in cerebrospinal fluid pressure with a fall of general arterial pressure and a rise in internal jugular venous pressure. Since amyl nitrite causes a vasodilatation of the blood vessels of the brain, it is believed that the rise in spinal fluid pressure follows the increased brain volume caused by vasodilatation.

3. Solution of pituitary causes a rise in cerebrospinal fluid and internal jugular venous pressures. The arterial pressure drops. It is difficult to explain the rise in cerebrospinal fluid pressure in the case of this drug, since there is a conflict of opinion as to whether the vessels of the brain are dilated or constricted.

4. Histamine causes a very sharp rise in cerebrospinal fluid pressure with a moderate to slight drop of arterial pressure and no change in jugular venous pressure, thus forming an exception to the rule that cerebrospinal fluid pressure and intracranial venous pressure are linked together. The explanation may be that this drug has a definite secretory effect on the choroid plexus, or that there may be a vasodilatation with an increased flow of blood through the brain, thus increasing the brain volume without increasing the internal jugular venous pressure.

5. Caffeine sodium citrate causes a drop of cerebrospinal fluid pressure with very little change either in the internal jugular venous or the general arterial pressure. The explanation may be that the diuretic effect of caffeine, by lessening the blood volume, causes this drop.

SPECIAL ARTICLE

CAUSES OF EPILEPSY

STANLEY COBB, M.D.
BOSTON

Before beginning any discussion it is important to define the terms to be used, and it is especially important, as in this case, when there is lack of unanimity concerning the meaning of the principal term. "Epilepsy" is here considered as meaning the sudden and repeated appearance of seizures of which convulsive movements or loss of consciousness, or both, are the principal elements.

Thus, attacks of the "grand mal" type and of the "petit mal" type are looked on as similar, differing only in degree. And the seizure itself is considered as a symptom entirely analogous to such a symptom as headache. In searching for its cause, therefore, one looks for a simpler mechanism than in looking for the etiology of a disease, or of a syndrome, for the seizure must be due to a phenomenon that may occur in many pathologic states. If a list is prepared of the different pathologic bodily states in which seizures may occur, the result is enlightening (fig. 1). In the first place, the list is long; secondly, it is varied and contains many conditions that appear to have little in common with one another; finally, certain groups may be made out of this list on the basis of a probable similarity of the mechanism involved in producing the seizure. If there are enough data to make such a grouping allowable, the grouping is significant and important because it takes one out of the primitive state of medicine (observation and classification) into the more enlightened state where one attempts to understand physiologic mechanisms, giving hope of eventually reaching the point where physics and chemistry will answer the query "what causes a fit?"

HEREDITY

In making the various possible groups, one of the most important is that of the inheritable diseases or states that are associated with epilepsy. In most of the older writings there is far too much emphasis

Submitted for publication, Jan. 2, 1932.
From the Neurological Unit of the Boston City Hospital and the Department of Neuropathology, Harvard Medical School, Boston.
Aided by a grant from the Harvard Epilepsy Commission.
Read at a meeting of the Philadelphia Neurological Society, Oct. 23, 1931.

on the inheritance of epilepsy. For example, Davenport [1] advised segregation of all epileptic persons during their whole reproductive period (from the 15th to the 45th year) and estimated that if this were done, epilepsy would be practically eliminated from the population in fifty years. Such an attitude probably arises from two main

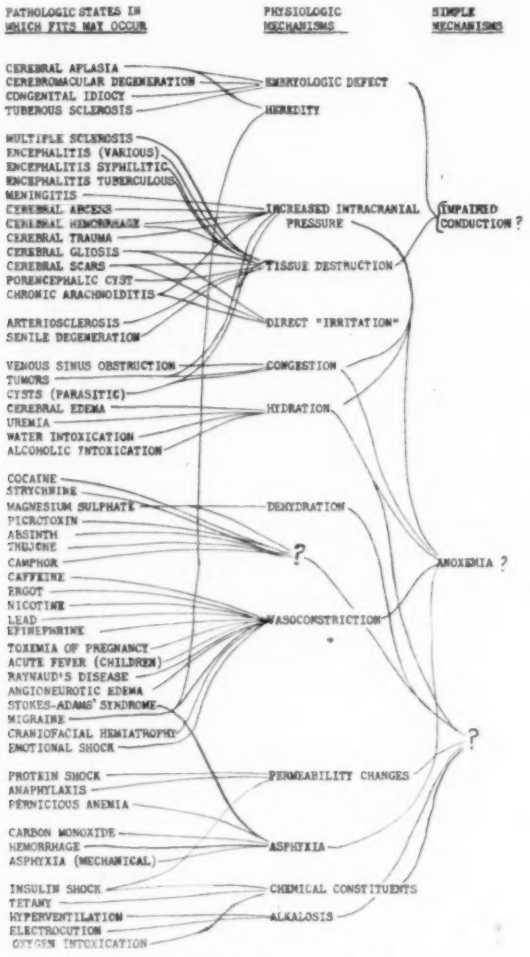


Fig. 1.—Pathologic bodily states in which fits may occur.

errors: (1) looking on epilepsy as a disease, and (2) working entirely with institutionalized epileptic patients. Lennox and I (with the aid of a great number of neurologists who have generously helped by sending us data) have compiled statistics concerning the inheritance of epilepsy on a new basis. For each person studied, the parents, siblings

1. Davenport, C., and Weeks, D. F.: J. Nerv. & Ment. Dis. **38**:641, 1911.

and children are listed; the total numbers (for each category of person studied) are added together, and the number that have suffered from seizures or migraine noted. The result is expressed as the number of epileptic or migrainous relatives per thousand. Thus, it was found that related to a group of 250 normal controls there were 1,896 parents, siblings and offsprings. Of these, only 2.6 per thousand suffered from epilepsy, whereas in a group of 1,086 epileptic persons (nontraumatic and noninstitutionalized) with 9,139 relatives, there were 21 per thousand cases of epilepsy in these near relatives. In a group of 235 patients with epilepsy who had suffered head trauma, there were only 14 per thousand epileptic relatives. In statistics from state hospitals there are very much higher percentages of inherited taint. Comparing this to the general morbidity rate for epilepsy in the population at large, which is estimated at 3 per thousand, it is seen that our control group was a little better than expected. That there is an inheritable taint is indicated by the fact that the general run of epileptic patients coming to the clinic have eight times as many epileptic relatives as the control group. The even higher figure for institutionalized patients is probably due to the fact that in hospitals for epilepsy many of the patients are congenitally feebleminded, a condition known to be inheritable.

The close connection between epilepsy and migraine has been often noted. Ely [2] showed recently that the inheritance of migraine is often associated with the appearance of epilepsy. Our statistics show that of the relatives of the normal control group, 15 per thousand had migraine; while of the relatives of the epileptic patients (noninstitutional and nontraumatic) 43 per thousand suffered from migraine. It is interesting that even the relatives of traumatic epileptic patients showed a high percentage of migraine, 22 per thousand. Taking into consideration the fact that of patients with known brain trauma only about 4 per cent develop seizures, and that in cases of brain tumor only between 21.6 per cent [3] and 30 per cent [4] have convulsions, it is evident that in addition to the cerebral injury (inflammation, neoplasm, gliosis or scar), there must be some constitutional factor in people who develop seizures. That this is latent in many people who never develop seizures is more than probable. Hence it is impossible to prevent the inheritance of epilepsy by preventing the marriage of epileptic persons or by sterilizing them; for the many "silent carriers" of the tendency are just as eugenically dangerous as the people who actually have fits. In fact, more epilepsy is found among the children of migrainous parents than among the children of epileptic parents.

2. Ely, F. A.: The Migraine-Epilepsy Syndrome: A Statistical Study of Heredity, Arch. Neurol. & Psychiat. **24**:943 (Nov.) 1930.

3. Parker, H. L.: Epileptiform Convulsions, Arch. Neurol. & Psychiat. **23**: 1032 (May) 1930.

4. Sargent, P.: Brain **44**:312 (Nov.) 1921.

INCREASED INTRACRANIAL PRESSURE

The next group that may be chosen from the list is a large one, taking in the acute infections of the brain and meninges. These often cause convulsions, usually in the acute stages when there is increased intracranial pressure, but this cannot be the only mechanism at work, for convulsions do occur when the intracranial pressure is low. A few experiments indicate that animals with increased intracranial pressure are more susceptible to convulsant drugs than normal animals or animals with low intracranial pressure.[5] Tower,[6] however, found no lowering of the threshold to electrical stimulation in animals with high pressure. A study of the histories of patients with brain tumor shows that only about 25 per cent of them had convulsive seizures, and these are the patients with tumors in the anterior fossa of the skull. In other words, the high pressure produced by tumors of the posterior fossa rarely brings on convulsions.[3]

Irritation is a word used to cover much ignorance. No one knows just what is meant by irritation of a nerve cell. Abnormal fluids bathing the cell may stimulate it (strychnine solutions painted onto the cortex are known to cause convulsions), and excessive electrical stimulation regularly precipitates local convulsions. In connection with inflammation, there is always edema; increased permeability of capillary walls may be a factor. Nevertheless, it is better to avoid this word because it, as yet, denotes no physiologic mechanism.

DESTRUCTION OF CEREBRAL TISSUES AND "SHORT-CIRCUITING"

In chronic encephalitis, or postencephalitic states, there may be gliosis of the brain and the formation of connective tissue scars. These, too, are said to "irritate" nerve cells and cause abnormal discharges, but by just what mechanism no one knows. Cerebral hemorrhage and trauma may act in much the same way, causing reactions in the brain that resemble encephalitis but are not truly inflammatory. Here must be mentioned the contracting scars described by Foerster and Penfield.[7] Also, chronic diseases, such as multiple sclerosis, may cause seizures; the plaques are gliotic and rarely show contraction. It may be that an important factor in all these extensive lesions is destruction of axis cylinders and a reduction of the number of available association pathways for nerve impulses to travel. This, theoretically, could cause a "short-circuiting" of afferent impulses, so that they reflexly discharge over efferent tracts without the normal delay caused by spreading

5. Pike, F. H., and Elsberg, C. A.: Am. J. Physiol. **76**:593 (May) 1926.
6. Tower, S. S.: Bull. Johns Hopkins Hosp. **43**:237 (Oct.) 1928.
7. Foerster, O., and Penfield, Wilder: Brain **53**:99 (July) 1930

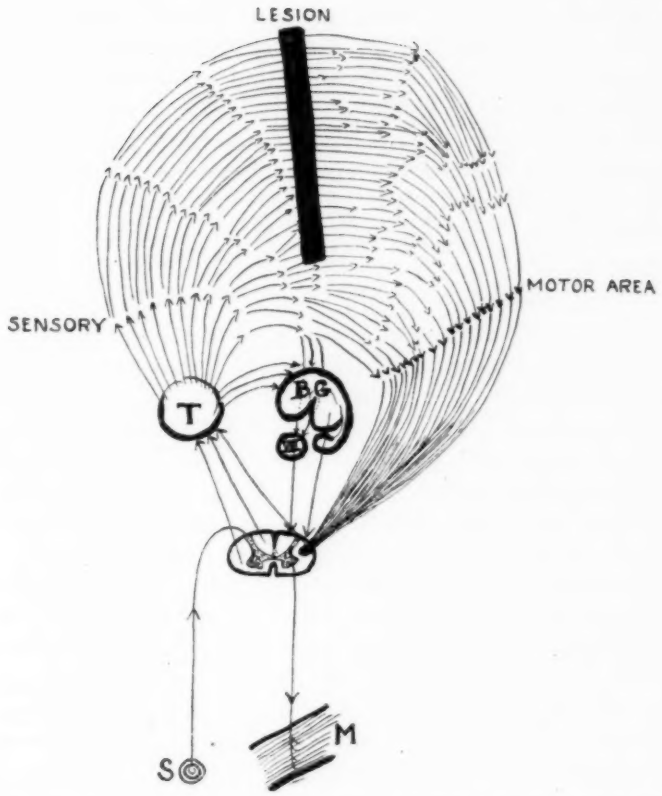


Fig. 2.—Diagram to illustrate how a lesion interrupting association paths in the cortex cerebri might cause "short-circuiting" and explosive discharges with convulsion. The afferent stimuli enter the sense organ (*S*), pass to the spinal cord and are relayed to the thalamus (*T*). From here they go along various paths, largely to the sensory postcentral area of the cortex, and thence spread out over innumerable association paths in the cerebral hemispheres. This spreading causes normal delayed response and inhibits sudden motor reaction (Cobb: Arch. Neurol. & Psychiat. **19**:981 [June] 1928). It might be that a lesion interrupting many association fibers, like the one indicated, would cause a "short-circuiting" of the afferent impulses across the remaining association paths. These on reaching the motor area of the cortex might set up a sudden explosive reaction externalized in the muscles as a convulsion.

through the wide association areas of the cortex (fig. 2). Such short-circuited discharges might well be explosive and disorderly and cause seizures of various sorts.[8]

Other chronic processes, such as arteriosclerosis, senile degeneration, chronic arachnoiditis and porencephalic cysts, may also cause seizures by tissue destruction and this "short-circuiting" mechanism. Tumors and cysts obviously cause increased intracranial pressure and damage to the tissue, but the facts that tumors of the hind-brain rarely if ever cause convulsions, and that convulsions are most common when the mortor cortex is involved, indicate that there may be something in the idea of direct irritation. It might be that these tumors interfere with circulation and cause local stasis with edema, anoxemia and softening.[9] Such changes have been reported at autopsy. Moreover, when circulation is slowed and oxygen supply is only just sufficient, slight vasoconstriction might cause anoxemia enough to precipitate a seizure.

HYDRATION, EDEMA AND DEHYDRATION

Another important group of convulsions are found in states in which there is known to be edema of the brain or increase in the amount of cerebrospinal fluid in the ventriculo-arachnoid system. The most obvious of these conditions is the intoxication caused by forcing large amounts of water by stomach tube;[10] animals thus treated show, among other abnormalities, convulsions and cerebral edema, with increased intracranial pressure. Likewise, animals given large doses of distilled water intravenously[11] showed cerebral edema at autopsy. In man, the commonest causes of edema of the brain are trauma, uremia and alcoholism, but edema occurs when no causative factor is known. Recently, Fay[12] and McQuarrie[13] did a great deal of work on the influence of water balance on the frequency of seizures in epileptic patients. Fay advanced a "mechanical theory of epilepsy," which holds that epilepsy has a "hydraulic" pathology. He believed that "the *predisposing factor* concerned with a *major convulsive seizure* is due to a hydration state." In cases in which there has been injury to the

8. Southard, E. E.: Am. J. Insanity **64**:607 (April) 1908. Lennox, W. G., and Cobb, Stanley: Epilepsy, Baltimore, Williams & Wilkins, 1928.

9. Gibbs, F. A.: Localization of Brain Tumors, Arch. Neurol. & Psychiat., in press.

10. Rowntree, L. G.: J. Pharmacol. & Exper. Therap. **29**:135 (Oct.) 1926.

11. Weed, L. H., and Wegefarth, P.: J. Pharmacol. & Exper. Therap. **13**:317 (July) 1919.

12. Fay, Temple: Am. J. Psychiat. **8**:783 (March) 1929; Generalized Pressure Atrophy of the Brain Secondary to Traumatic and Pathologic Involvement of Pacchionian Bodies, J. A. M. A. **94**:245 (Jan. 25) 1930.

13. McQuarrie, Irvine: Epilepsy in Children: The Relation of Water Balance to the Occurrence of Seizures, Am. J. Dis. Child. **38**:451 (Sept.) 1929.

arachnoid villi by inflammation or trauma, Fay[14] stated that "the resultant delay in the escape of cerebrospinal fluid consequent on this injury may produce overfilling of the subarachnoid channels over the frontoparietal area and supracortical increase in pressure, favoring a relative ischemia and progressive cortical atrophy."

No one doubts that abnormal accumulations of cerebrospinal fluid in the arachnoid space are a common observation in the brains of epileptic persons. But that these accumulations of fluid can result from "supracortical increase in pressure" leading to "cortical atrophy," I emphatically deny. The main source of cerebrospinal fluid is from the choroid plexuses within the ventricles. Thence the fluid *flows* out into the arachnoid space to be absorbed largely by the arachnoid villi over the vertex and partly by the small venules and capillaries of the arachnoid space. Note the word *"flows."* This means that pressure must be higher in the ventricles than in the arachnoid space about the cisterna magna, and lowest of all in the region of absorption over the vertex. Otherwise there would be no flow.

If obstruction to the pathways of absorption occurs, it will lead immediately to a rise in cerebrospinal fluid pressure, not only in the subarachnoid space but also in the ventricles. The flow of cerebrospinal fluid will be slowed, and the pressure gradient from ventricle to subarachnoid space will be reduced; but as long as any cerebrospinal fluid is absorbed, some flow will continue; and as long as there is flow, the pressure must be greater in the ventricles than in the subarachnoid space. If the obstruction at the arachnoid villi becomes complete, the flow will cease, and then pressure in the arachnoid space will become equal to that in the ventricles. There is, however, no known mechanism by which the pressure could become greater in the subarachnoid space over the cortex than in the ventricles. This fundamental fallacy in Fay's "mechanical theory of epilepsy" was first pointed out by Fremont-Smith.[15]

The conditions already outlined are well illustrated in meningitis in which the exudate obstructs the absorption bed. The resulting hydrocephalus is always internal. In fact, all hydrocephalus resulting from increased pressure must be internal, and although the pressure may rise higher and higher, the pressure within the ventricles always is greater than that outside in the arachnoid space. The continued rise is possible because the increase in cerebrospinal fluid pressure is reflected on the veins of the choroid plexus, compressing them, raising the capillary pressure in the choroid plexus and thus maintaining an

14. Fay (footnote 12, second reference).

15. Fremont-Smith, Frank: Epilepsy and the Convulsive State, Baltimore, Williams & Wilkins, 1931, p. 617.

effective filtration pressure in the choroid plexus in face of a rising intracranial pressure. This mechanism, which explains the continued formation of cerebrospinal fluid leading to progressive internal hydrocephalus in the presence of marked intracranial pressure, has been described by Fremont-Smith.[16] Thus, in hydrocephalus from pressure the surface of the cortex is pressed up against the dura and skull. In patients in whom there is "external hydrocephalus" the pressure is usually normal. This is the case in persons with epilepsy. In 400 cases measured by Lennox in our clinic, 71 per cent were within normal limits (from 100 to 200 mm. of spinal fluid); 17 per cent were between 200 and 250 mm. of water and 8 per cent were low (less than 100 mm.).

"External hydrocephalus" results from cerebral atrophy in the presence of normal intracranial pressure. Cerebral atrophy regularly leads to external as well as internal hydrocephalus. For instance, thrombosis of a branch of the middle cerebral artery causes softening, with later a dilatation of one ventricle and atrophy of the overlying cerebral convolutions with localized "external hydrocephalus" replacing the atrophied brain substance. Such accumulations of fluid follow atrophy from any cause (inflammatory, traumatic, degenerative, vascular) but are, as in the majority of persons with epilepsy, associated with normal cerebrospinal fluid pressure. It is my belief that the cortical atrophy found in epileptic patients is a primary lesion (caused by the various aforementioned inflammatory and reparative mechanisms) and that the accumulation of fluid in the arachnoid spaces over this atrophy is merely a space-filling mechanism,[17] a hydrops ex vacuo, following shrinking of the tissues, or filling up congenital defects. That an accumulation of fluid could cause local pressure on the cortex and atrophy seems to me utterly impossible within such a hydraulic system as there is in the cranial cavity.

Fay further expressed the belief, although he produced no evidence to substantiate it, that water drinking raises the intracranial pressure in persons with epilepsy and that water restriction leads to lower intracranial pressure. The extraordinary constancy of the composition and volume of the blood and the great adaptability of the kidneys in maintaining this constancy, make one question such an idea unless well substantiated by actual measurements of pressure. Were the kidneys of epileptic patients unable to excrete water normally, such changes in pressure might occur. Fremont-Smith,[18] however, tested the diuretic

16. Fremont-Smith, Frank: Nature of Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **17**:317 (March) 1927.

17. Dandy, W. E.: Bull. Johns Hopkins Hosp. **34**:245 (Aug.) 1923.

18. Fremont-Smith, Frank: New York Neurol. Soc., Dec. 1, 1931, Arch. Neurol. & Psychiat., in press.

response to water drinking in fifteen patients with epilepsy as well as in normal persons. In three of the epileptic patients there was some delay in the excretion of water. In only one of these three did a convulsion occur following the test (drinking 1,200 cc. of water in three hours). These data, together with the many studies showing normal renal function in epileptic patients, place the burden of proof on those who claim that water drinking can increase intracranial pressure. They will have to produce evidence that decreased excreting power of the kidneys is a frequent finding in epilepsy.

In two epileptic patients, Lennox and Fremont-Smith made the following observations: Lumbar puncture was done after the patients had fasted overnight after a period of normal fluid intake. Pressures were read every minute for from thirty to forty-five minutes to secure a good base line. In one patient a liter of water was then drunk as rapidly as possible; in the other 200 cc. was drunk each half hour to a total of 1,200 cc. The spinal fluid pressures were read continuously throughout this procedure and for some time afterward. No appreciable rise in cerebrospinal fluid pressure occurred. Before the pressure readings were discontinued, both patients had excreted in the urine more than the whole volume of water ingested.

In these same two patients, lumbar punctures were done after several days of rigid restriction of fluid and again after several days of forcing fluids from 3 to 5 liters of water per day. The spinal fluid pressures obtained by three punctures on each patient, i. e., during the period of normal fluid intake after fluid restriction and after forcing fluids, showed no appreciable variation.

I do not deny that water restriction may be beneficial to some patients, or that water drinking may in some increase the number of seizures, but I do deny that the restriction is beneficial through lowering intracranial pressure or that the drinking is harmful through raising it. Fay's mechanical theory of epilepsy is unsound on theoretical grounds, while his assumptions as to the influence of water drinking on cerebrospinal fluid pressure are proved to be erroneous by the direct experiments of Fremont-Smith and Lennox that are at present going on in our laboratory.

VASOCONSTRICTION

A large group of clinical causes of fits is the one that takes in various drugs and pathologic states that either affect the sympathetic nervous system or the blood vessels directly. It has recently been demonstrated by Penfield [19] that the vessels within the brain, as well as the pial vessels,[20] have a sympathetic innervation. Forbes and

19. Penfield, Wilder: Proc. Am. Neurol. Soc., 1931, p. 426.

20. Stöhr, P.: Mikroskopische Anatomie des vegetativen Nervensystems, Berlin, Julius Springer, 1928.

Wolff [21] and Cobb [22] recently reviewed the old evidence and brought new proof that there is a vasomotor control over the cerebral vessels. Much clinical evidence goes to show that some fits are preceded by cerebral vasoconstriction.[23] Observation of vasoconstriction in the eyegrounds by Jackson, and the ordinary clinical observation in some cases of facial pallor at the onset of a convulsion, bring additional evidence. Against this is the absence of a fall of spinal fluid pressure before petit mal attacks. The convulsant drugs, caffeine, ergot, nicotine and camphor, and lead poisoning all have been observed to cause vasoconstriction. There is good histologic evidence that many convulsions, including puerperal eclampsia, are due to vascular spasm in the brain.[24] Some cases of Raynaud's disease and of angioneurotic edema are accompanied by seizures. Two arguments against the theory of anemia are brought out by Wilson:[25] first, that the epileptic fit comes on suddenly, and that the convulsions due to asphyxia (including anemia from cardiac and vascular disease) come on more slowly. Second, many phenomena known to be due to cerebral ischemia may take place without convulsion or interference with consciousness (hemiplegia from an arterial thrombosis, etc.). All one may say in the present state of knowledge is that cerebral anemia can and does cause epileptiform seizures. The emotional element in many cases is obvious, at least as a precipitating factor; many a patient will tell how his seizures are brought on by emotional stress. The observation that convulsions may be precipitated by emotional stress has a theoretical explanation in physiologic mechanisms. Fright, anger and other strong emotions are known to cause pallor of the face and changes in blood circulation elsewhere in the body. Cannon [26] showed that a dog barking at a cat causes many such changes in the cat. Tracy [27] discussed fright as a cause of epilepsy. Benedek [28] stated that large doses of epinephrine cause convulsions in rabbits, and Kussmaul and Tenner [29] caused them

21. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

22. Cobb, Stanley: Am. J. M. Sc. **178**:528 (Oct.) 1929.

23. Foerster, O.: Deutsche Ztschr. f. Nervenh. **94**:15 (Dec.) 1926. Fay (footnote 12, first reference).

24. Spielmeyer, Walter: The Anatomic Substratum of the Convulsive State, Arch. Neurol. & Psychiat. **23**:869 (May) 1930.

25. Wilson, S. A. K.: Modern Problems in Neurology, London, E. Arnold & Co., 1928.

26. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton & Company, 1929.

27. Tracy, R. B.: Northwest Med. **26**:188 (April) 1927.

28. Benedek, L.: Wien. klin. Wchnschr. **31**:1365, 1918.

29. Kussmaul, Adolf; and Tenner, Adolf: Epileptiform Convulsions Caused by Profuse Bleeding and Also True Epilepsy, translated by Edward Bronner, New Sydenham Society, London, 1859.

by faradizing the cervical sympathetic. Severe emotion with its resulting vasoconstriction might cause a brief, sudden reduction of oxygen in the human brain. For example, a boy, previously frightened several times by dogs, was observed to have a fit, with signs of "organic" change in the brain (Babinski's sign) when accidentally barked at by a dog in our laboratory. Thus, once more the line vanishes between "functional" and "organic." In fact, as Bastian said to Wilson,[30] "Did you ever see a fit that was not functional?"

ANOXEMIA

There are five conditions on the list that obviously work through anoxemia of the brain. All of these five cause widespread anoxemia and convulsions. The first is Stokes-Adams syndrome in which, as reported by Mackenzie,[31] if the heart block lasted for ten seconds only unconsciousness alone occurred, but if it lasted for seventeen seconds there was also convulsion. The onset of paroxysmal tachycardia may also be attended by seizures. The other two mechanisms that can be relied on regularly to produce convulsions are carbon monoxide poisoning and mechanical asphyxia, as in strangulation. Moreover, convulsions not rarely occur in pernicious anemia, at the end of excessive hemorrhage and from compression of the carotids in arteriosclerotic subjects.[32] Here is an important group that appears to act through anoxemia of the nerve cells. Add to this the vasoconstriction group and the mechanism of anoxemia appears to be numerically the most important precipitating cause of clinical convulsions. In experimental animals it is always possible to produce convulsions by ligating the arteries that supply the brain, and also by limiting the oxygen that is inhaled. In the latter procedure, a degree of oxygen lack that will not affect normal persons will produce a seizure in some epileptic persons.[9] There is no other method of producing convulsions that is as regularly demonstrable. It is therefore worth while to study with great care all those conditions that might give a widespread and rapid reduction in oxygen supply to the brain, because, even if this is only one of many causes of seizures, yet it is a mechanism that might yield to treatment.

PERMEABILITY CHANGES

The convulsions of anaphylaxis and those following protein shock are well known. There is evidence that these convulsions and also

30. Wilson, S. A. K.: Brit. M. J. **2:1** (July 3) 1926.

31. Mackenzie, J.: Diseases of the Heart, London, Oxford University Press, 1918.

32. Riesman, D., and Fitz-Hugh, T.: Tr. A. Am. Physicians **42**:356, 1927; Ann. Int. Med. **1**:273 (Nov.) 1927.

those occurring in insulin shock may be caused by changes in the permeability of the walls of the nerve cells or of the capillaries.

ALKALOSIS

Hyperventilation may precipitate seizures in epileptic persons or cause spasms like those observed in tetany. The seizures are explainable on the change in the acid-base relationship or on the low calcium content in the blood. Likewise, various other of the pathologic states enumerated might be explained on changes in chemical constituents rather than on any obvious physiologic change. For example, the convulsions observed after poisoning due to magnesium sulphate and those following insulin shock may be explained chemically, but one cannot as yet even postulate the mechanism; the best physical chemists deprecate the premature use of their data by clinicians.

SUMMARY

Fifty-six clinical causes of fits have been grouped and discussed. Thirteen physiologic mechanisms have been postulated to explain the occurrence of these seizures. To simplify further and relate seizures to one or two simple mechanisms will be the work of years of further research. At present one might tentatively reduce the number of mechanisms by saying that it seems probable that embryologic defect and tissue destruction act by altering neural conduction. Congestion, vasoconstriction, asphyxia and increased intracranial pressure might all act by means of cerebral anoxemia. This includes thirty-three of the fifty-six causes given, and makes the largest group. Hydration and dehydration probably act through chemical changes (e. g., acid-base relationships), and the mechanical theory that they act by pressure is controverted. A large group of drugs and chemicals, apparently quite unrelated in other ways, cause convulsions by some entirely unknown mechanism. There is still much research to be done before one can explain the cause of a fit.

ABSTRACT OF DISCUSSION

DR. W. G. SPILLER, Philadelphia: The recognition of the grand mal and the petit mal attacks as essentially indicative of the same disorder receives general approval. More questionable is the character of the jacksonian attack but in my judgment it cannot be sharply separated from the general convulsion, which may begin as a jacksonian attack. Dr. Frazier and I have had some cases of jacksonian epilepsy in which operation has not revealed a focal lesion, and yet often such a lesion is found.

As regards heredity, it is interesting to note that from the statistics that Dr. Cobb has analyzed of nontraumatic and noninstitutionalized cases of epilepsy there were only 21 per thousand cases of epilepsy in near relatives, and yet this was eight times as great as in his normal controls. If one turns to a book too

seldom read in these days, Sir William R. Gowers' "Manual of Diseases of the Nervous System," one finds that he regarded heredity as present in 35 per cent of cases of epilepsy; he included insanity as a factor in heredity. In Dr. Cobb's normal control group, 15 per thousand of the relatives had migraine, while in the epileptic group it was found in 43 per thousand. He finds that more epilepsy occurs among the children of migrainous parents than among the children of epileptic persons. When I published a paper on the relation of migraine to epilepsy in 1900, I did not attack the problem by the statistical method, but I presented arguments and referred to cases that must make the thoughtful man acknowledge that a relation probably exists.

It is true that no one knows exactly what is meant by "irritation" of a nerve cell, but as the term is commonly used it implies that certain agents have the power to increase the function of the nerve cell, and if it is a motor cell excessive movement is caused. If Dr. Cobb will give us a better word we shall use it.

Dr. Cobb's group of convulsions caused by vasoconstriction with the emotional element as a precipitating factor is one of the most interesting of his classification. The case he reports in which fear of a dog brought on an epileptic attack is an interesting illustrative case. We may come to learn that some of the manifestations of grave hysteria, such as the severe convulsive seizures with opisthotonus suggesting decerebrate rigidity, may belong here.

Dr. E. Spiegel, Philadelphia: One interesting problem in this paper is the relation of pressure between the ventricle and the cisterna cerebellomedullaris. Dr. Cobb is right that the pressure must be higher in the ventricle than in the cisterna to cause a flow out of the ventricle. But I think that the pressure can change much in the cisterna under different conditions, not only due to the movements of the head and respiration but also to different positions of the spine, etc. If there is a constant flow toward the cisterna it would never be possible to get ascending iodized poppy seed oil 40 per cent into the ventricle following injection into the lumbar region. Another interesting point is that different factors here may give rise to epilepsy, but only in some persons. Only a small group of traumatic persons, for instance, have epilepsy. In some dogs it is easier to produce these convulsions, and in others it is more difficult. There must be some unknown "constitutional" factor in epilepsy, which must be sought in the nerve cells.

This brings me to the last group of Dr. Cobb, the primitive physical mechanisms. If one innervates the skeletal muscles from the cortex by voluntary impulse, a series of impulses follow so quickly that the mechanical effect looks continuous (tonic). The same occurs if the motor area of a man or a mammal is stimulated by slight faradic stimuli. Why is quite a different form of discharge obtained, a rhythmic interruption of the impulses sent out by the cortex, in pathologic conditions or following stronger or repeated cortical stimulation? The simplest explanation for these rhythmic phenomena is the refractory period, the short period of loss of excitability following each impulse. Since the experiments of Broca and Richet, it is known that there exists also a refractory period for the cortex. The phenomena of the refractory period alone are not sufficient to explain the clonus following cortical stimulation under special conditions. It is a normal phenomenon which alone does not explain the difference between normal and pathologic forms of reaction.

It is interesting from this point of view to study simple objects. Dr. Osterbout, in the Rockefeller Institute, studied Nitello flexilis in which one large cell forms the organism. He injured the cell with a solution of potassium chloride, and if he applied a low concentration there was only one discharge recorded by the string galvanometer. If he increased the concentration, he did not get a single but a

rhythmic discharge. In nerve fibers, a weak direct current has no effect so long as it remains constant. But if a strong current is applied a rhythmic discharge (Garten, Ebbecke) results. This rhythm is independent of the refractory period.

These observations are easily understood by the modern theories of irritation, which state that the excitable cells or fibers have semipermeable membranes on the surface of which an electric potential exists. If a strong stimulus acts on the membrane, it becomes a little perforated, and the electric potential is lowered. A local current flows from the normal neighborhood to the injured place and stimulates the cell. After some time, the perforation of the membrane progresses so far that the potential of the stimulated area is lowered enough to produce a new local stimulating current from the neighborhood (Ebbecke). Thus, the progressive injury of the membrane causes in intervals local currents and rhythmic excitation independent of the refractory period. We do not know what happens in the nerve cells, but one might suppose that the pathologic overexcitability in epilepsy has to do with an abnormally low resistance of the cell membranes to stimuli. In any case, the experiments mentioned show that rhythmic discharges can be produced on very different types of cells or fibers by constant stimuli, independent of the refractory period.

Dr. Temple Fay, Philadelphia: Dr. Cobb stated the neurologic conditions that are associated at times with convulsions, and has placed the major portion of them into the groups wherein edema, increased intracranial pressure and anoxemia play such an important rôle.

In the hereditary group, there are present definite vascular anomalies, especially on the venous side, which are complicating factors, and which we have been able to demonstrate during the past two years by measurement of the jugular foramen. They are frequently inadequate, and may be responsible for passive congestion of the brain, due to poor venous elimination, especially when unusual positions of the head and neck are assumed. This type of obstruction leads to both edema and anoxemia.

The question as to the arbitrary adoption of limits of normal intracranial pressure seems to be the crux of the situation, and Dr. Cobb's and our point of view will be found to coincide closely should this factor be established. Dr. Cobb accepts the reading of from 100 to 190 mm. of water as the normal range of intracranial pressure. This would mean, translated into the standard of mercury, that from 7 to 14 mm. of mercury represent the normal intracranial pressure. I seriously doubt the wide variation and in my experience, covering 3,000 lumbar punctures, from 6 to 10 mm. of mercury represent the limits of normal in the child as well as in the adult, 8 being the usual figure, and readings above 10 mm. of mercury are considered as definite evidence of increased intracranial pressure.

Recently, in a discussion of these values, I pointed out to Fremont-Smith the error in capillarity of the water manometer, and on investigation it was found that the water manometer had a 25 mm. of water capillarity, which was unrecognized as recently as April, 1931. The result of this investigation was followed by a notice of correction from the manufacturers, so that this may be responsible for the high readings accepted by Cobb as normal. If one subtracts the capillarity error of the water manometer of Cobb's readings, one will find that his measurement of pressure, in the 400 cases reported, falls in the top-normal and increased pressure groups, as we have maintained, and thus our contention that a low-grade intracranial pressure is present in the majority of epileptics remains unchanged.

Dr. Cobb has offered a formula of pressure, based on the laws of hydraulics, in support of the view that pressure within the ventricles at the source of spinal fluid must be greater than pressure at the outlets, which are assumed to be along the

longitudinal sinus at the vertex. The formula is based on the assumption that there is a "flow" of spinal fluid from the ventricles to the outlets, and second that the craniovertebral cavity is a closed system, in order to apply the laws of hydraulics. I believe that much doubt may be directed against the assumption that an "actual flow" occurs within the cerebrospinal fluid system. Certainly, fluid is produced and absorbed, but the amount of turnover in twenty-four hours is relatively small when the total volume of fluid is considered. We have established, during the past two years, that patients placed on a dry diet and 600 cc. of total fluid intake per day fail to produce spinal fluid after the second day, so that a "dry tap," or only 1 or 2 cc., may be obtained when complete drainage, with the patient in the horizontal position, is attempted. On the other hand, if the patient is given the same diet and placed on 900 cc. of fluid, from 45 to 65 cc. of spinal fluid may be obtained at each drainage every twenty-four hours. The relative amount produced with higher levels of fluid, and in uncontrolled cases, is conjectural. On the 900 cc. level, the patient at best produces only one third of the total cerebrospinal fluid volume, and if a "flow" is present it is imperceptible. The fluid "seeps into" the ventricular system as a dialysate, and again "seeps out" into the venous channels at the vertex. The condition is similar to that of a spring of water on a hill side. Water enters and leaves the spring, but there is no possible way of demonstrating a "flow" and the physiologic apparatus now at our disposal would fail to demonstrate the slightest change of pressure between the "source" and the "outlet." A "flow" implies a gradient, and certainly no gradient can be demonstrated within the cerebrospinal fluid system, with its varying positions during the activities of the subject, in both the erect and prone positions. Again, the analogy of a large lake might be suggested, where the inlet and outlet of fluid are definitely demonstrable, and yet within the body of water itself a "flow" would be difficult to demonstrate, although certain currents of fluid might be produced by the force of addition of fluid at the inlet. There is no rush of fluid at the source of ventricular fluid production, and there are no demonstrable falls or cataracts at the outlet. The question of "flow" within the cerebrospinal fluid system is therefore open to grave doubt, and there appears to be only the imperceptible diffusing of fluid through the general subarachnoid system itself, with fluid "seeping" in and out of the entire system, without demonstrable currents being established.

The laws of hydraulics regarding a closed system are also open to modification, and Dr. Cobb's formula would therefore not seem to apply to the craniovertebral cavity. The craniovertebral cavity is capable of being "open" to a definite degree by large venous outlets, not only the jugulars but also the perivertebral and peridural sinuses. These modify and quicky correct the many slight changes of intracranial pressure within the hydraulic system itself.

It must be clearly borne in mind that the craniovertebral cavity contains three components that make up its total volume: (1) arteriovenous blood, containing the volume within the arteries, veins, capillaries and sinuses; (2) brain and meningeal structures composed of cellular elements, and (3) cerebrospinal and perivascular fluid. Spinal fluid pressure represents the interplay between these three volume components, and one must not overlook that the pressure represents the volume ratios, in a sense. It is evident that if the craniovertebral cavity were suddenly closed, one could not introduce even 1 cc. more of fluid without rupture of the container, as this is the fundamental law of hydraulics, and of uncompressible fluid within a completely filled and enclosed system. If, however, 10 cc. of fluid is added to the cerebrospinal fluid volume and 10 cc. of venous blood squeezed out of the large sinuses, the resulting pressure would be the same as if the original volume ratios were equal, but the physiology in terms of circulating blood volume, and consequently available oxygen, would be definitely altered.

Brain tumors and cerebral edema occur without producing an increase in intracranial pressure, and although the volume and mass of the brain may be definitely increased by the new growth, an equal volume of blood and spinal fluid has given way before this addition, so that the pressure relationships remain the same. It is only when there is a definite increase of the volume components beyond the levels of compensation by the other two that a rise in intracranial pressure can be expected, and with such a rise there is an hydraulic compression of the surface capillarity circulation, with consequent anoxemia. This we believe to be the force for the characteristic atrophy of the brain, always adjacent to the fluid surfaces, and that the relative increase of fluid in cases of atrophy is due to hydraulic compression, and not simply "space compensation." As Dr. Winkelman pointed out, chronic anoxemia produces a scattered loss of ganglion cells, and consequently of associated white matter, so that shrinkage of the brain follows secondarily.

It is evident that the tremendous atrophy of the brain due to dilatation of the ventricles in an internal hydrocephalus could not be explained on an idiopathic atrophy, in which the fluids simply filled the cavity after the brain had symmetrically contracted, leaving the dilatation of the ventricular cavities. In the internal hydrocephalic group, the obstruction is demonstrable, and the increase of pressure is beyond doubt. There is also demonstrable in the so-called communicating type of hydrocephalus, or hydrocephalus ex vacuo, a low grade increase of pressure which may be augmented from time to time by exertion and other activities, and the end-result is in proportion to the prolongation and degree of pressure. We believe, therefore, that spinal pressure readings must be standardized by an accepted manometric reading and that the patient must be standardized in terms of diet and fluid, before a true normal may be established.

The fact that no recognition of the shift in volume relationships in terms of pressure has been undertaken makes it evident that we cannot accept a normal or a top-normal spinal pressure reading as evidence that there is no disturbance of one of the three volume factors within the craniovertebral cavity. For instance, a patient with an excess of 100 cc. of spinal fluid over the normal may have a spinal pressure of only 10 mm., which would be considered a top-normal from our point of view. This pressure indicates that the balance between the three volume relationships is practically balanced, but as far as the physiologic and pathologic conditions are concerned there is no doubt but that a great change has occurred in the important structures of the brain.

We must consider spinal fluid pressure readings in the light of volume relationships, because in the end it is the volume relationships that concern us, and the disturbance of physiologic function may be profound when one volume component has been increased at the expense of another even though the spinal pressure may remain within the range of normal figures.

Dr. Cobb indicated his belief that inhibitory areas are diminished in the epileptic patient, owing to the various pathologic processes, and that there is a "short circuit" between the sensory stimulus and the motor response responsible for the convulsion itself. There can be no doubt that this is probably the factor responsible for the sudden explosion, but it must be assumed that either the inhibitory field is temporarily wiped out or that an unusual stimulus must occur to produce a seizure. That the actual pathologic disturbance of the nervous structures is not responsible for the "variant" seems evident, in that the patient is carefully controlled between attacks. Otherwise, a continuous "short circuit" would be expected. However, in the presence of an already disturbed inhibitory mechanism a temporary rise in intracranial pressure or the loss of oxygen to the inhibitory field might lower the threshold to such a degree that ordinary stimuli could explode

the motor area, otherwise adequately protected. Here again it requires the superaddition of a physiologic change, and that change necessarily prompt.

We believe that the increase in fluid within the cranial cavity displaces important blood volume, and consequently oxygen, so as to predispose the patient to the seizure; that by controlling the volume of spinal fluid production it is possible to maintain the optimal circulation within the brain and thus obviate a periodic circulatory disturbance that may contribute to the direct motor response, which is termed a convulsion. For some reason many have believed that if fluid limitation helps to prevent the seizure, then the giving of large quantities of water should precipitate more frequent attacks. It is not the volume of water consumed by the patient that disturbs the intracranial balance, but it is the volume of fluid retained within the tissues and subarachnoid system that becomes important, and this is dependent on local disturbances in fluid drainage as well as general disturbances in renal and other portals of elimination.

In diabetes insipidus, the patient consumes huge amounts of fluid, but passes not only the amount ingested, but also frequently loses water from his tissues, so that the paradox of dehydration may be seen in the presence of an apparent attempted hydration. Gamble pointed out that water metabolism is dependent on certain fixed bases and carbohydrate metabolism, and that when fluid is not properly eliminated, in the presence of increased ingestion, there is likely to be induced an epileptogenic state. A balance of intake and output, along with the daily weight of the patient, becomes the most important consideration, and not the question as to the actual volume of fluids consumed. When output is not known, no conclusions can be drawn as to the influence of the volume of fluid ingested.

Dr. Cobb indicated that he believes that "oxygen lack" is probably the most important factor in the production of the convulsive seizure. In my opinion, much information may be gained from his group of Stokes-Adams' disease, and the time element registered between heart beats, in their relation to cases with convulsive seizures. If "oxygen lack" alone were the factor involved, one would expect a convulsive seizure as a terminal manifestation in every case of natural death. Thus, terminal states associated with convulsions are in the majority of cases also complicated by the process of venous stasis, such as cardiac decompensation, strangulation and sudden occlusion of the venous return from the brain, producing an immediate rise in intracranial pressure along with edema and passive congestion.

It must not be overlooked that a motor cell requires oxygen to maintain its function, either normally or in the violent form of a convulsion, and that it could not persist in its motor manifestations for many seconds after oxygen had been denied it. Therefore, we must hypothecate a degree of oxygen sufficient to maintain a violent and prolonged function of the cortex, without sufficient oxygen to supply the levels of consciousness, and conversely, oxygen content must be above the threshold of motor function, otherwise complete stupor and paralysis would supervene.

I am sure that if the pressure mechanisms were clarified and the volume relationships correlated, we would find that Dr. Cobb's views and our own are not far apart. I think that we are all agreed as to the existence of a predisposing factor and that this must be followed by a precipitating factor to bring on a typical major convulsion.

DR. COBB: Dr. Spiller has brought out some interesting points in relation to heredity. As to the word "irritation," I think it a perfectly good word and want no better, but I urge that we use it with humility, recognizing our ignorance of what the mechanism involved may be.

In answer to Dr. Spiegel, I would say that ascending iodized oil, being distinctly lighter than cerebrospinal fluid, could rise into the ventricle quite rapidly in spite of a slow outward cerebrospinal fluid flow through the aqueduct and lower ventricles. One often sees air bubbles rising up through water that is slowly flowing down a glass tube. In my paper I warned against the too precocious use of new physicochemical data, but I do think that Dr. Spiegel's remarks about the "primitive physical mechanisms" are interesting as speculations and even as prophecies. His use of the word "tonic" and "clonic" is too arbitrary. In a paper in *Brain*, in 1924, I discussed this, and in my papers on electromyographic studies of clonus (*Bull. Johns Hopkins Hosp.* **29**:247 [Nov.] 1918) and of tremor (*Bull. Johns Hopkins Hosp.* **33**:35 [Feb.] 1919) I discussed rhythmic discharge and its relationship to refractory period. The refractory period of cortical neurons is far too short to have any direct relationship with clinical clonus.

In answer to Dr. Fay, I would say that the arbitrary limits of normal intracranial pressure are difficult to establish. Dr. Fay (*J. Nerv. & Ment. Dis.* **71**: 481 [May] 1930) stated that a pressure of from 10 to 12 mm. of mercury should be considered as high normal. Now, however, he stated that readings above 10 mm. of mercury should be considered as evidence of increased intracranial pressure. He is quite right that the water manometer has a slight positive error due to capillary attraction, which varies between 15 and 25 mm. of water, depending on slight variations in the bore of manometers used. This means then that the pressures recorded with the water manometer are, on the average, 20 mm. of water higher than the true reading. It should be remembered, however, that there is another error, also slight, but in the opposite direction, due to the fluid displaced into the manometer system. This error tends to make the pressure reading too low and must compensate in part for the error due to capillary attraction. We may state then that the pressures as measured in a water manometer are somewhat less than 20 mm. of water too high i. e., about 1 mm. of mercury too high. It should be remembered also that very slight variations in the position of the patient or in the degree of relaxation of the patient will make greater errors in the pressure than this. One cannot, therefore, set any arbitrary line as being the uppermost limit of normal for spinal fluid pressure, any more than one can for blood pressure or any other physical measurement. Nevertheless, if one takes Dr. Fay's highest figure for normal as 12 mm. of mercury, which is equivalent to 163 mm. of water, and add 20 mm. of water for capillary attraction, 183 mm. of water is obtained as the upper level of normal pressure.

Ayer, as well as Fremont-Smith, considered 200 mm. of water as the upper limit of normal spinal fluid pressure when measured in the water manometer. This is only 17 mm. of water higher than 183, or Fay's figure. It will be seen, therefore, that there is no significant difference between our upper limits of normal and his. In the paper just referred to, Dr. Fay stated that in his 100 cases of epilepsy the average pressure was 11.2 mm. of mercury. This is within Fay's uppermost limit of normal and is equivalent to 172 mm. of water as measured in the water manometer, and therefore well within our uppermost limit of normal. Lennox, using the water manometer, has found the average pressure in 375 cases of epilepsy to be 186 mm. of water. This is very close to Dr. Fay's average figure of 172 mm. of water. It is therefore evident that Dr. Fay and ourselves are using very nearly the same upper limits of normal and that our average figures for the epileptic group are essentially the same. We would agree with him that the average pressure in epileptic persons is in the upper portion of the normal range, but we cannot agree with him that this constitutes an elevated intracranial pressure.

As to the flow of cerebrospinal fluid, I do not agree with Dr. Fay that this fluid is absorbed only along the longitudinal sinus; other sinuses have villi and some fluid is undoubtedly absorbed by the venules in the subarachnoid space. I do not see any use in arguing about "actual flow;" if there is formation at one point and absorption at another there must be flow between those points. As long as any movement of fluid takes place from ventricles to subarachnoid space, a pressure gradient must be present. It is inevitable that the pressure at the source within the ventricles should be greater than the pressure at the outlet in the subarachnoid space. If the flow is slight the pressure gradient will be slight, but if flow occurs at all the pressure gradient must exist. In a lake this movement of fluid may be slight, but it can be detected by physical methods. When the lake is frozen over, and thus in a partial closed box, the flow will be more marked.

Dr. Fay said that "the amount of turnover in 24 hours is relatively small." I believe that normally from 2 to 3 liters of fluid is produced by the choroid and absorbed into the meningeal veins in twenty-four hours. I consider this a relatively large "turnover." I do not think that the evidence justifies Dr. Fay's statement that "patients placed on a dry diet and 600 cc. of total fluid intake per day *fail to produce spinal fluid* after the second day."

There is another misconception of Dr. Fay's. This is in regard to the intracranial volume relations. Whereas he stated correctly that an increase in cerebrospinal fluid volume might be compensated for by the squeezing of an equal volume of venous blood out of the sinuses and thus leaving the original pressure unchanged, he overlooked the fact (Fremont-Smith: personal communication) that this cannot be true in the living organism with a continuous flow of blood through these venous sinuses, because as soon as the venous sinuses begin to be compressed and diminished in volume, the resistance to blood flow through them will become increased. This will automatically raise the pressure in the veins and also in the whole capillary bed of the brain, including the capillary bed of the choroid plexus. Such increased venous and capillary pressures will tend to dilate these vessels and also will give a greater filtration pressure in the choroid plexus. Both these factors will raise intracranial pressure. Therefore, any compression of venous sinuses or other obstruction to the outflow of blood from the cranium will be associated with increased intracranial pressure. This is beautifully illustrated by the prompt rise in intracranial pressure that results from the least compression of the jugular veins. Dr. Fay's idea of compensating the increased cerebrospinal fluid volume by diminished venous blood volume in the cranial cavity without increase in pressure might work in a dead system, but does not work in the living organism.

These are the main points in which we disagree with Dr. Fay's conception of the physics as well as of the physiology of intracranial pressure. His criticism of the "oxygen lack" theory, that if it were the main factor one would see a convulsion just before every "natural death," I can answer by a comparison with our experimental animals. These are anesthetized with amytal before operation; they go on for hours with fairly normal vegetative functions, but we cannot produce convulsions in them. I believe that most people just before death are in a partially anesthetized state due to many profound systemic changes—for example, acidosis, which we know inhibits convulsions. Were they quite normal otherwise and died of cessation of heart beat, I believe they all would exhibit a terminal convulsion.

Obituary

JAMES HENDRIE LLOYD, M.D.

1853-1932

James Hendrie Lloyd, son of Enos Morris Lloyd and Julia (Hendrie) (Lloyd) was born in Doylestown, Pa., Dec. 1, 1853. He died of septic pneumonia at the Presbyterian Hospital, March 14, 1932. His father was an attorney at law. He was the fourth of a line of physicians in his mother's family. His greatgrandfather, grandfather and maternal uncle were medical men. He was prepared for college at Wyer's Academy, West Chester, Pa., and received from Princton the A.B. in 1873 and A.M. in 1876. He studied law in his father's office for two years after graduating from college and then, deciding that his real ambition was to be a physician, entered the medical school of the University of Pennsylvania, graduating in 1878. In 1879, he married Miss Susan Newell. They had four children, two sons and two daughters, of whom three survive, Captain J. Paul Lloyd, U. S. A., W. Hendrie Lloyd of Philadelphia and Miss Marion Lloyd.

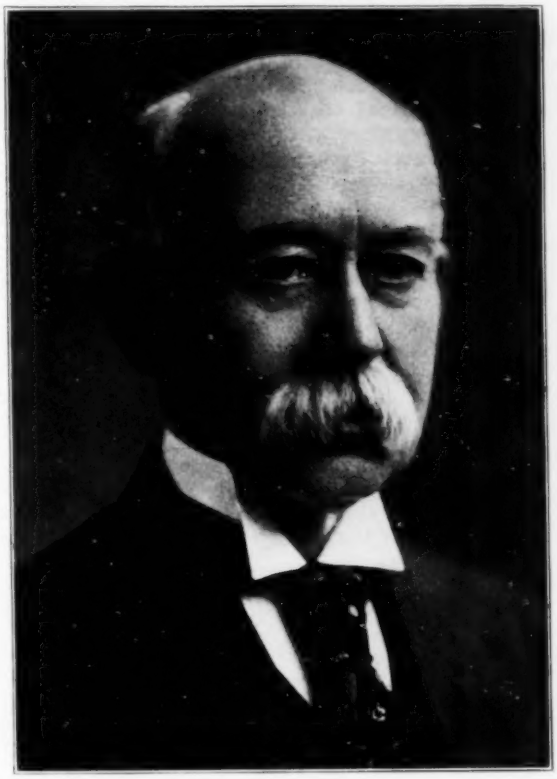
Dr. Lloyd became a member of the American Neurological Association in 1886 and its president in 1899. He was also president of the Philadelphia Neurological Society and member of the Philadelphia Psychiatric Society. He was very active in these societies and read many papers before them. He was at one time a member of the consultant staff of the Wernersville State Hospital for the chronic insane and of the Elwyn Training School for feebleminded children. He also belonged to the county, state and national societies, and became a fellow of the College of Physicians of Philadelphia in 1886.

He held many hospital positions. He was appointed visiting neurologist to the Methodist Episcopal Hospital at the time of its foundation and served for thirty-five years. He was appointed neurologist to the Philadelphia General Hospital in 1888, resigned after serving a number of years, was reappointed, and again resigned in 1925. He was for years professor of neurology in the Graduate School of Medicine.

He was editor of the *Philadelphia Medical Journal* from 1901 till 1903. He wrote a great deal on neurologic, psychiatric and medicolegal subjects. He also wrote two very useful and interesting popular essays published in *Scribner's Magazine*, one entitled "Mental Contagion and Popular Crazes," the other, "The Incorrigible Optimist." Some of his most important work in medicolegal jurisprudence appeared in the fifth edition (1905) of Wharton and Stille's "Medical Jurisprudence."

Dr. Lloyd was much more than a mere man of medicine. He did not believe in the recent American idea, that a specialist should know all about one organ of the human body and nothing about any other

organ. On the contrary, he believed that a specialist should first be a well trained physician and simply devote especial attention to some one part of the body. Furthermore, he was born with scholarly instincts and seized every opportunity to feed his intellectual hunger. He had wide cultural interests and was one of the best read men among my friends. Medicine to him was not a money-making trade but a profession that he deliberately chose, and to which he had, if I may be permitted to use



JAMES HENDRIE LLOYD, M.D.
1853-1932

a theological term, a positive call. He suffered for years from a physical handicap. During middle life he began to be hard of hearing, and in his later years was completely deaf. He carried his burden uncomplainingly, and was an exception to the rule, that the deaf become peevish and suspicious. He was neither. He was a splendid example of a high type, a type which some of us think, or at least fear, is becoming less frequent as "demos" is growing more powerful and changing the ideals of the world.

CHARLES W. BURR, M.D.

Book Reviews

Les phénomènes de répercussivité (système sympathique; système cérébrospinal; les spasmes vasculaires; épilepsie; asthme). By André-Thomas. Price, 32 francs. Pp. 243. Paris: Masson & Cie, 1929.

Various functions in the organism are interdependent. A disturbance of one of these functions reflects on the others. The repercussion of a disturbance from a diseased organ on the other organs is known as "sympathy." When, vice versa, the normal physiologic activity of an organ reflects on the functions of the diseased organ, then one may speak of this particular susceptibility of the latter as of a phenomenon of repercussion. André-Thomas studies: (1) the phenomena of repercussion occurring within and through the medium of the sympathetic nervous system—pilomotor, sudoral and vasomotor repercussions; (2) the phenomena of cerebrospinal, motor and sensory repercussions—chorea, athetosis, myoclonus, tremors, muscular fibrillations, so-called epilepsy of amputation stumps, phenomena of echo-pain, causalgias, sensory hallucinations of amputated extremities, etc. The phenomena discussed in these two chapters of the book are relatively easy to demonstrate, and their nature and the rôle of the repercussion in their mechanism are well established. On the grounds of the phenomena of repercussion, as observed in the sphere of sympathetic and cerebrospinal functions, one might attempt to study more complex conditions, the clinical manifestations of which suggest that there also it deals with repercussion. Thus, the author discusses the phenomena of repercussion apparent in pathologic states characterized by vascular spasm: intermittent claudication, angina pectoris, Raynaud's disease, spasm of the central retinal artery and migraine. Then he studies at length the rôle of repercussion in jacksonian and generalized epilepsy and in asthma. The book is closed by a chapter containing general considerations on the phenomena of repercussion.

The common feature in all manifestations of repercussion is a special elective susceptibility of one or another apparatus of the organism to react to the stimulations of a specific quality to which this apparatus became attuned under the influence of various factors, such as humoral disturbances, neurovegetative constitutional imbalance and central or peripheral lesions. The author insists that the phenomena of repercussion are highly individual reactions, often peculiar to the given subject. The state of specific reactive ability of the affected apparatus is influenced by a wide range of factors, internal and external to the organism—temperature, atmospheric pressure and certain physiologic states, such as menstruation, exertion and emotional and affective stimulations. The last mentioned seem to be especially prominent in the mechanism of repercussion; so the goose-skin and hair-bristling (pilomotor reflex) are intimately connected with the manifestation of emotional and affective states. Usually generalized and bilateral, in some conditions they might become more prominent on one side or part of the body. The same is true with regard to the sudoral and vasomotor repercussions. André-Thomas cites the case of a patient in whom, following an injury in the region of the eyebrow, a sudoral and vasomotor reaction developed, which spread over the homolateral side of the face whenever the patient ate certain spiced foods (specific gustatory stimulation). Sometimes a representation of a specific sensation combined with an emotional state may provoke exaggerated perspiration of the part of the body that previously suffered an injury. In the mechanism of such reaction a principle of Pavlov's conditioned reflexes may be at play. The rôle of the psychic influences and of the individual constitutional background is even more prominent in the phenomena of vasomotor repercussion. The author discusses the

semeiology of the phenomena of the vasomotor repercussion and their relationship to those so far unexplained trophic disturbances which follow sometimes slight injuries of extremities and which were described during and after the World War by Babinski and Froment, Sicard, Roussy and others (atrophies, contractures and circulatory and trophic disturbances). The apparatus of the pupillary reflex offers a special case of sympathetic repercussion. The dilatation of the pupil on the side of the intrathoracic lesion (Roque's pupillary sign in cases of apical tuberculosis, emphysema and pleuritis) may be regarded as a phenomenon of sympathetic repercussion. The asymmetry of midriatic reaction to cocaine or atropine in such cases seems to be a phenomenon analogous to repercussion; the pupils, sensitized by sympathetic irritation, react to the toxic action of the drug more actively and more promptly on the diseased than on the unaffected side. The repercussion in the centers directly irritated by an organic lesion is not limited to the sympathetic system; the phenomena of repercussion are often observed in lesions of the cerebrospinal centers. Just as the irritability of the sympathetic centers is not always the result of the lesion in their immediate vicinity but sometimes is caused by a lesion on the periphery, so certain peripheral lesions also reflect on the state of irritability of respective cerebrospinal centers. These centers thus become sensitized and begin to react to the central and peripheral stimulation to which they normally remain indifferent.

The author discusses the phenomena of repercussion in motor disturbances occurring in lesions of the central nervous system. Syringomyelia offers a particularly rich field for observation. For example, the myofascicular fibrillations are influenced by the pinching of a hyperesthetic zone of an extremity. Similar facts were observed in amyotrophic lateral sclerosis, chronic poliomyelitis and even in acute anterior poliomyelitis. Disagreeable or painful stimulation and exposure to cold cause accentuation of the fibrillary twitching. This phenomenon is yet more striking in unilateral muscular atrophy and when the atrophied muscles begin to twitch under the influence of stimulation of the normal side. Obviously it does not deal with an ordinary reflex. The author insists that the emotional tone is that quality of the stimulation which renders it particularly effective in producing phenomena of motor repercussion. The influence of affective and emotional stimulation in bringing about and increasing the motor agitation of patients with chorea, athetosis, tremor and myoclonus is confirmatory of this statement. The disease creates a state of special erethism in the nerve centers, and a minimal emotional influence, otherwise ineffective, now begins to provoke the outbreak of choreic movements. Though sensation appears to be indispensable for the production of a reflex, it is more through the affective tone with which the sensation is endowed than through its quality as a perception that such sensation produces the reflex reaction. The author compares this type of reactions with the hyperalgesic reflexes described by Babinski and Jarkowski in cases of Brown-Sequard's syndrome and in cerebral hemiplegia.

In the sensory sphere, the symptom of pain offers particularly demonstrable examples of cerebrospinal repercussion. Whatever may be the seat, the nature or the cause of the pain, its intensity and its quality in the same patient vary under the influence of different circumstances. Many types of pain, even when syphilis is not in question, are exaggerated at night. The influence of the warmth of the bed, the position of the affected part of the body or some biologic change in the organism induced by the state of sleep may provoke them. Such are, for example, acroparesthesias of the climacterium; on the other hand, patients suffering with arthritis are familiar with the influence of meteorological factors on the pain in the affected joints or in old wounds. Whatever the mechanism that controls the intermittent character of the painful paroxysm may be, one is compelled to attribute a peculiar reaction ability to the affected part of the body, which presents some analogy with the phenomena of repercussion. Circulatory disorders in the affected part seem to be an essential element in the mechanism of painful repercussion. The rôle of the nervous system (sympathetic) in the production of pain is prominent; however, one must count also the influence of humoral factors.

The symptom of pain, of whatever nature, is provoked or aggravated under the influence of a wide range of peripheral and central stimulations, including emotional and psycho-affective influences. This is a feature especially characteristic for the causalgic syndrome of Weir-Mitchell. As in motor repercussion one observes synkinesis, so in sensory repercussion one meets with the phenomenon of synesthesia, when following one localized stimulation two sensations are perceived. If such sensation is painful, one deals with synalgesia comparable to the echo-pains of Gubler. The author cites the case of a soldier in whom causalgia in the right foot followed an injury of the thigh; the attacks of pain in that foot were provoked or exaggerated by emotion, noise, rubbing of the hands or forehead or the contact of the unaffected foot with the sheets. In the course of a few weeks, these pain-producing zones disappeared and only rubbing of the healthy foot continued to elicit pains in the heel of the right foot, under condition that the integument of both feet was dry. The exaggeration of pains following peripheral stimulation and emotion is also observed in bulbar, pontile, peduncular and, especially, thalamic lesions. The author cites Head's case of thalamic syndrome, in which the thalamic pain was exaggerated on the affected side of the body whenever the patient heard sad songs, music, etc.

These sensory repercussion phenomena must not be confounded, however, with the associated or radiated sensations observed, for example, in the period of regeneration of the peripheral nerves. The mechanism of these radiating sensations is entirely different, and their clinical characters are also different. They can be explained as the result of an error of orientation of the regenerating nerve fibers; sometimes such error is a congenital defect. Also the phenomena of so-called referred pain of Mackenzie, observed in diseases of the visceral organs, are not identical with the phenomena of sensory repercussion and are more akin to the paresthesias observed during the regeneration of nerves. However, in some respects they may be comparable to the repercussion, as the latter may exaggerate the radiating or referred pain.

On the grounds of these observations and physiopathologic considerations, André-Thomas attempts to explain the mechanism of various vasculospasmodic syndromes, migraine, epilepsy and asthma. The text of the book is studded with numerous references and citations from personal and other observations. This makes the reading rather difficult; while struggling through the intricate labyrinth of facts, interpretations, hypotheses and comments, the reader sometimes loses track of the author's main idea. The book is interesting and instructive; it is a valuable essay in which the author attempts to elucidate phenomena that are usually left out of consideration by an observer, though they are unquestionably important and promise perhaps to throw new light on the pathogenesis of many obscure disease conditions and on the mechanism of symptoms associated with them.

God Helps Those. By Fritz Künkel, M.D. Price, $3.50. Pp. 279. New York: Ives Washburn, 1931.

Dr. Künkel brings to his work as psychiatrist a keen concern for problems philosophic and sociologic. Probably the most telling exponent of Alfred Adler's individual psychology in Berlin, his formulation comes as if from a different angle of vision and challenges, by reason of the unfamiliar perspective, to reexamination of the significance of ideas that, for all their worth, seem sometimes to be in danger of disregard through trite repetition.

The book under review is a sharply focused attempt to deal with the practical problem of learning to apply modern psychology to the everyday tasks of parents, teachers and the like. In the original it is entitled "Die Arbeit am Charakter." The keynote to the entire discussion lies in the single and ever repeated emphasis on self-education, on searching within oneself, in one's own veiled attitude of egocentrism (that takes form in fear, lack of confidence, personal authority, etc.), for an explanation of failures on the part of the child or the patient with whom one is dealing. How have you broken faith with him, shattered his trust? What

have you done to arouse his rebelliousness? What unsolved vanity or fear of your own hinders your discerning the normal impulse that lies hidden under his rôle of stupidity, unruliness and the like?

In the first chapter the author states briefly what he has come to regard as a fundamental formulation of the problem with which psychology has to deal, a formulation that he has treated more theoretically and at greater length in "Einführung in die Charakterkunde" ("Let's Be Normal," New York, Ives Washburn, 1929). As the "first law for the formation of human character," he says: "Understand that you are subject and object at one and the same time, that you are free and responsible, that you cannot escape the results of your hebavior, and that you must bear the results even of the escape from results." That is to say, all that we do consciously and by intent, but also every function whatever of our being, "arise from our subjectivity, our essentiality. They have their origin in the (no longer bodily) nucleus of man's being." The situation that confronts me may be as it will; in the final analysis it depends on me, on my own nucleus of being, how I respond, what I do with the situation. So far as my body is hit by a stone, I am object; but whether I weep or rage depends not on the blow but on me. Different persons would respond differently. Herein may be discerned the kernel of individuality and, as a corollary of most far-reaching import, the fact of self-responsibility. The demands inherent in this fact of responsibility—subjectivity—are so tremendous that one instinctively tries to dodge the issue by arguing that he is helpless as object—for example, of the stone—and is forced to respond in the manner for which he does not care to assume responsibility.

This twofold fact of being both object and subject is characteristic of every human relationship. Courageous acceptance of all that it implies constitutes the fullest living, makes possible learning, richness of experience and development—all that lies open to active participation, with the uncertainties of good and ill that this involves.

But for those who have learned fear instead of courage, the uncertainties and responsibilities of such a course seem too great. Two escapes offer: either to refuse to be object, and so to attempt to assert the domination of one's subjectivity whether through ruthless disregard of others or through aloofness as spectator free from all personal interest, or, on the other hand, to refuse to be subject, assumming the rôle of irresponsibility at any cost. But both attempts are falsifications of the actualities of life; the second rule concerns itself with detection of their presence and working in the individual.

The concluding section of this chapter discusses the difficulty of character study. In looking on any human being as "object"—of education, love or whatever the interest may be—one belies all the foregoing. This erroneous tendency must be seen and corrected or failure will result.

Chapter 2 pierces deeper into the question of purpose (Zweck) and aims (Ziele), the latter being understood as the partial and more immediate stages of human functioning on the way to the "final purpose" that is somehow life itself. What this ultimate purpose is, no one knows. "Directive lines" (Leitlinien) and "directive image" (Leitbild) have here adlerian signification. The distinction between causative and teleologic functioning is kept vividly in mind. As in the preceding chapter, and following throughout the book, each section is succinctly summarized in the form of a working rule; a method that results in the building up of a skeleton so clear and organically valid as to render the book usable in a most uncommon degree.

The chapter on unity illuminates still further the meaning of aim and purpose in character, and the relationship to them of contradictory traits and ambivalence.

The concluding section on "the superpersonal unity of life" reveals the author's religious attitude of faith that life is essentially good. It reminds one of Sartor Resartus in the emphasis on action. Essentially making for sanity, and the doctrine of many a great philosophy, it is none the less, along with them, open to challenge. On the other hand, the challenger who himself has courage

and will to do the best he can with life, even though his "faith" in any real "purpose" is quite lacking, will find himself in pragmatic accord with the rules of conduct.

Under the general title of "Education," book 2 opens with a study of the child in its relation to the mother, the relationship through which it acquires its foundational experiences of change, insecurity and deprivation and the concomitant awakening of its selfhood and self-preserving demands. These become fixed as "Leitlinien," the traits that help one to understand the "Leitbild," the latter being the interpretation, one might say, that the child feels of himself and life and the manner in which he can maintain his ego in such a world. The naiveté of initial community with the mother is lost; the problems of self and the world have begun.

Whether now through recalcitrance or docility, apparent stupidity or other habits, the way must be one of experimentation and learning. How can and ought the adult to help? What in his own attitude hinders? Over and again recurs the word "sachlich"—objective (once or twice rather too coldly translated as matter-of-fact)—objective concern with the problem, the actual situation, as against personally authoritative or emotional attempts. The child should be helped to understand his own tactics, his immediate aims, with reference to the deep underlying and unified purpose of the ego. He must learn how to be both subject and object. The adult's own balance is the surest aid.

Though the treatment of the theme "Adolescence" offers perhaps nothing especially new, it is none the less valuable for the clear sanity of presentation and for the manner in which it links the difficulties of this period to the preceding preparation of the child. The educator is warned against undertaking "a campaign of enlightenment" and again reminded to search in his own lack of courage and clarity for his inability to arouse courage, poise and patience in the child.

The solution of all these partial problems is possible only by reference to the goal of living that is permeated by a sense of real community (Gemeinschaft) within love and marriage, which must then itself become a social element in the community of society as a whole.

The goal—but it is realized in so small a degree. Is there a way out of the isolation that is the most important symptom of the mistaken education to self-centeredness? Yes, says Dr. Künkel, it is possible to educate oneself anew, and the way lies in discovering the relationship between one's suffering and one's self-centeredness. "The fruits which we can produce are the mirror in which we can read" what we need to know. Searching in this mirror we can no longer deceive ourselves through resort to our partial actions; there we may read the whole.

And yet the question how far one can reeducate himself with no assistance from another, how far the teachings of modern psychology are of themselves sufficient, is today still unanswered. A case is discussed in which the amount of personal aid received was very small in proportion to the results. Also a second case that goes to show how seriously the author takes the entire import of his book: Search for the error in yourself—also where you are not succeeding with the treatment of your patient. Specifically he warns: Our theory is no magic means to cure. It can only teach to counteract hindrances to normal development. He says that "this activity and the special attitude it demands cannot be taught. The development of this attitude and the success of this work is always, in every case and even in every hour, a creative act, a productive process of spiritual growth which must always anew be hoped for, awaited and risked, for the appearance of which one can do nothing except to try to free oneself from all claims, demands, fears and attempts at escape."

It is a book of uncommon earnestness, and the clearness of formulation would seem to be the outcome of an essentially integrated view. The English edition does not bear the name of the translator, and is so free from the wooden-legged movement of many translations from the German that it would seem to have been prepared by the author himself or directly under his supervision. Occasionally

the word chosen conveys a slightly false sense of the original, but the only dire error that has come to the reviewer's eye is the substitution of importance for impotence (p. 21, line 4).

Der Genius im Kinde. By G. F. Hartlaub. Price, 20 marks. Pp. 229. Breslau: Ferdinand Hirt, 1930.

This is a revised and expanded edition of Hartlaub's work bearing the same title, which was published in 1921. The first chapter of the earlier edition on "The Worship of the Child" has been omitted as no longer necessary. Other parts have been eliminated and many sections elaborated. A notable addition is the increased number of illustrations. These have been taken from the permanent collection of the Archives of Children's Drawings in the Mannheim Municipal Art Gallery. There are 123 in all, 52 being drawings by children from the ages of 3 to 9, 65 drawings by children from 10 to 16 years of age and 6 by persons from 17 to 22 years of age.

The purpose of the book is to reveal the development of artistic ability in children as it is manifested in drawing and painting. The author bases his study on an analysis of the series of illustrations presented. He claims significance for the study as giving insight into the origins of art, social psychology, child psychology and art education.

The first claim depends on acceptance of the theory of recapitulation. Common elements in the art of primitive peoples and that of children are described in a most interesting way. The view of the psychology of childhood presented combines the older ideas of the child study period in this country with Freud's view of the psychology of art.

Hartlaub believes that adolescence is marked by great changes in the individual. He attaches much importance to the study of children's drawings, because it is difficult to investigate the dreams of little children and one can study scientifically their inner life through its manifestation by paint brush and pencil. The dream child is so closely related to the play child that play products in art can give knowledge of the child mind and particularly of the nature of the art impulse in childhood.

The most valuable contribution of the book is in the field of art education. The series of illustrations, which are beautifully reproduced, is itself of great interest. The analysis of their characteristic features is illuminating. The pedagogic principles that are advocated by the author to guide the art training of small children are timely and sound. One of these, namely, that the "play way" should be followed in learning in art work, is well known in America and has been applied for over a decade in progressive schools. It is in elaborating how the play impulse functions in art education that Hartlaub is especially felicitous.

He contends that the child's natural self-expression in drawing and painting is essentially akin in purpose and method of attack to that of the great artist. Instead of strengthening this tendency, however, art teachers in the past have been apt to destroy it by imposing adult technic of symbolic representation on children. Hartlaub stresses the point that there is now evidence that the unschooled child has a sense of balance, symmetry, proportion and harmony as early as 3 years of age, though color for him means unbroken, bright, fundamental color and not distinctions of shade and tone.

The discussion of the color consciousness of the child and of the nature of ornamental decoration in his handiwork is particularly good. Teachers of children in the primary grades would find much of interest in this book. To psychologists its value is limited to affording a series of drawings and paintings showing the development of the child in this field, and to giving a sample of what freudian theory has to suggest in the field of education.

The book is interesting throughout and is extremely attractive in its external features.

Les tumeurs des centres nerveux et des nerfs périphériques: atlas du cancer. By Gustave Roussy and Charles Oberling. Volumes 9 and 10. Price, 80 francs. Pp. 48, with 12 colored plates: Paris: Félix Alcan, 1931.

This atlas of the tumors of the central nervous system and peripheral nerves presents the French classification of the gliomas. The work is beautifully illustrated with many colored drawings and has an adequate discussion of the plates. The tumors of the central nervous system are much more completely treated than those of the peripheral nerves.

The tumors of the central nervous system are divided into: (1) gliomas, (2) ependymochoroidal tumors, (3) ganglioneuromas, (4) neurospongiomas and (5) neuro-epitheliomas. The gliomas are again divided into: (1) astrocytomas, (2) oligodendrocytomas and (3) glioblastomas, or gliomes à cellules indifférenciées.

Roussy and Oberling do not accept the division of astrocytomas into protoplasmic and fibrillary. They prefer to divide them into astrocytome très fibrillaire, astrocytomes peu fibrillaires or afibrillaires and astrocytomes giganto-cellulaires. They describe also a pseudopapillary astrocytoma, which from the description and illustrations would seem to be an astroblastoma. The oligodendrocytomas are similar to those described by Bailey and Cushing, Bailey and Bucy, and Kwan and Alpers. They include among them "mucous gliomas," and state that such tumors are composed of oligogliocytes. The glioblastomas are similar in all respects to those described by Bailey and Cushing, and Globus and Strauss.

The ependymal tumors are divided into two groups: (1) ependymomas and (2) ependymogliomas. The former have two subgroups: ependymoblastomas and ependymocytomas. These correspond to the tumors of Bailey. The ependymogliomas are found in the region of the fourth ventricle, aqueduct, medulla and cord. They are characterized by the presence of ependymal and astrocytic elements, the proportions of the two elements varying considerably. The neurospongiomas correspond to the medulloblastomas of Bailey and Cushing.

The atlas is decidedly worth having, and will be useful and beneficial to those interested in the pathology of brain tumors.

Grundzüge der Entwicklungsgeschichte der Menschen in vergleichender Darstellung. By Dr. Richard Weissenberg. Twelfth edition. Price, 15 marks. Pp. 435. Leipzig: Georg Thieme, 1931.

It is only rarely that a medical book has the honor of having more than two or three editions, yet this work has reached its twelfth. This in itself is a measure of its need and success. This edition is considerably larger than the last. It is of great interest to neurologists, for it gives the development not only of the nervous system, but of every other part of the body. In that it differs from most books of this sort. The illustrations are excellent, and the colored plates are well reproduced.

Arbeit und Gesundheit. Part 17. Sammlung aerztlicher Gutachten. Edited by Professor Martineck. Price, 6 marks. Pp. 295. Berlin: Reimar Hobbing, 1931.

This book contains a series of clinical observations by various authors. It is of some interest to neurologists, for there is reference to such conditions as thrombo-angiitis obliterans, poliomyelitis, encephalitis, multiple sclerosis, and so on. The reports, however, are so scanty that they are not of great scientific interest.